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(54) **PARTIALLY SATURATED TRICYCLIC COMPOUNDS AND METHODS OF MAKING AND USING SAME**

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(57) **ABSTRACT**

The invention provides tricyclic compounds and their use in treating medical disorders, such as obesity. Pharmaceutical compositions and methods of making various tricyclic compounds are provided. The compounds are contemplated to have activity against methionyl aminopeptidase 2.

12 Claims, No Drawings

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PARTIALLY SATURATED TRICYCLIC COMPOUNDS AND METHODS OF MAKING AND USING SAME

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a national stage filing under 35 U.S.C. §371 of PCT/US2012/036789, filed May 7, 2012, which claims priority to U.S. Ser. No. 61/483,257 filed May 6, 2011 and U.S. Ser. No. 61/559,856 filed Nov. 15, 2011, all of which are incorporated by reference in their entirety.

BACKGROUND

Over 1.1 billion people worldwide are reported to be overweight. Obesity is estimated to affect over 90 million people in the United States alone. Twenty-five percent of the population in the United States over the age of twenty is considered clinically obese. While being overweight or obese presents problems (for example restriction of mobility, discomfort in tight spaces such as theater or airplane seats, social difficulties, etc.), these conditions, in particular clinical obesity, affect other aspects of health, i.e., diseases and other adverse health conditions associated with, exacerbated by, or precipitated by being overweight or obese. The estimated mortality from obesity-related conditions in the United States is over 300,000 annually (O'Brien et al. Amer J Surgery (2002) 184:4S-8S; and Hill et al. (1998) Science, 280:1371).

There is no curative treatment for being overweight or obese. Traditional pharmacotherapies for treating an overweight or obese subject, such as serotonin and noradrenergic re-uptake inhibitors, noradrenergic re-uptake inhibitors, selective serotonin re-uptake inhibitors, intestinal lipase inhibitors, or surgeries such as stomach stapling or gastric banding, have been shown to provide minimal short-term benefits or significant rates of relapse, and have further shown harmful side-effects to patients.

MetAP2 encodes a protein that functions at least in part by enzymatically removing the amino terminal methionine residue from certain newly translated proteins such as glyceraldehyde-3-phosphate dehydrogenase (Warder et al. (2008) *J Proteome Res* 7:4807). Increased expression of the MetAP2 gene has been historically associated with various forms of cancer. Molecules inhibiting the enzymatic activity of MetAP2 have been identified and have been explored for their utility in the treatment of various tumor types (Wang et al. (2003) Cancer Res. 63:7861) and infectious diseases such as microsporidiosis, leishmaniasis, and malaria (Zhang et al. (2002) J. Biomed. Sci. 9:34). Notably, inhibition of MetAP2 activity in obese and obese-diabetic animals leads to a reduction in body weight in part by increasing the oxidation of fat and in part by reducing the consumption of food (Rupnick et al. (2002) Proc. Natl. Acad. Sci. USA 99:10730).

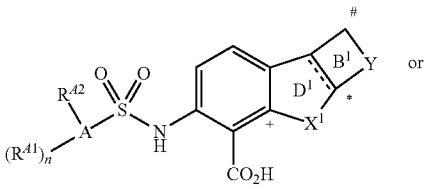
Such MetAP2 inhibitors may be useful as well for patients with excess adiposity and conditions related to adiposity including type 2 diabetes, hepatic steatosis, and cardiovascular disease (via e.g. ameliorating insulin resistance, reducing hepatic lipid content, and reducing cardiac workload). Accordingly, compounds capable of modulating MetAP2 are needed to address the treatment of obesity and related diseases as well as other ailments favorably responsive to MetAP2 modulator treatment.

SUMMARY

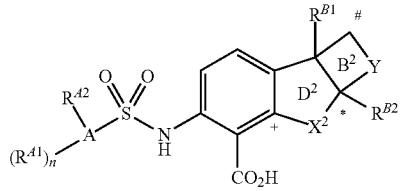
The invention provides, for example, compounds which may be modulators of MetAP2, and their use as medicinal agents, processes for their preparation, and pharmaceutical compositions containing them as an active ingredient both alone or in combination with other agents, as well as provides for their use as medicaments and/or in the manufacture of medicaments for the inhibition of MetAP2 activity in warm-blooded animals such as humans. In particular this invention relates to compounds useful for the treatment of obesity, type 2 diabetes, and other obesity-associated conditions. Also provided are pharmaceutical compositions comprising at least one disclosed compound and a pharmaceutically acceptable carrier.

In an embodiment, provided herein are compounds represented by formula I and II:

Formula I



Formula II



or pharmaceutically acceptable salts, stereoisomers, esters or prodrugs thereof, where A, B^1, B^2, D^1, D^2, R^{A1}, R^{A2}, R^{B1}, R^{B2}, Y, X^1, X^2, A and n are as defined herein.

DETAILED DESCRIPTION

The features and other details of the disclosure will now be more particularly described. Before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

DEFINITIONS

"Treating" includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.

The term "alkenyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond. Exemplary alkenyl groups include, but are not limited to, a straight or branched group of 2-6 or 3-4 carbon atoms, referred to herein as C_{2-6}alkenyl, and C_{3-4}alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc.

The term "alkoxy" as used herein refers to a straight or branched alkyl group attached to oxygen (alkyl-O—). Exemplary alkoxy groups include, but are not limited to, alkoxy groups of 1-6 or 2-6 carbon atoms, referred to herein as C_{1-6}alkoxy, and C_{2-6}alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.

The term "alkoxyalkyl" as used herein refers to a straight or branched alkyl group attached to oxygen, attached to a second straight or branched alkyl group (alkyl-O-alkyl-). Exemplary alkoxyalkyl groups include, but are not limited to, alkoxyalkyl groups in which each of the alkyl groups independently contains 1-6 carbon atoms, referred to herein as C_{1-6}alkoxy-C_{1-6}alkyl. Exemplary alkoxyalkyl groups include, but are not limited to methoxymethyl, 2-methoxyethyl, 1-methoxyethyl, 2-methoxypropyl, ethoxymethyl, 2-isopropoxyethyl etc.

The term "alkyoxycarbonyl" as used herein refers to a straight or branched alkyl group attached to oxygen, attached to a carbonyl group (alkyl-O—C(O)—). Exemplary alkoxycarbonyl groups include, but are not limited to, alkoxycarbonyl groups of 1-6 carbon atoms, referred to herein as C_{1-6}alkoxycarbonyl. Exemplary alkoxycarbonyl groups include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, etc.

The term "alkenyloxy" used herein refers to a straight or branched alkenyl group attached to oxygen (alkenyl-O—). Exemplary alkenyloxy groups include, but are not limited to, groups with an alkenyl group of 3-6 carbon atoms, referred to herein as C_{3-6}alkenyloxy. Exemplary "alkenyloxy" groups include, but are not limited to allyloxy, butenyloxy, etc.

The term "alkynyloxy" used herein refers to a straight or branched alkynyl group attached to oxygen (alkynyl-O). Exemplary alkynyloxy groups include, but are not limited to, groups with an alkynyl group of 3-6 carbon atoms, referred to herein as C_{3-6}alkynyloxy. Exemplary alkynyloxy groups include, but are not limited to, propynyloxy, butynyloxy, etc.

The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon. Exemplary alkyl groups include, but are not limited to, straight or branched hydrocarbons of 1-6, 1-4, or 1-3 carbon atoms, referred to herein as C_{1-6}alkyl, C_{1-4}alkyl, and C_{1-3}alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-butyl, 3-methyl-2-butyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.

The term "alkylcarbonyl" as used herein refers to a straight or branched alkyl group attached to a carbonyl group (alkyl-C(O)—). Exemplary alkylcarbonyl groups include, but are not limited to, alkylcarbonyl groups of 1-6 atoms, referred to herein as C_{1-6}alkylcarbonyl groups. Exemplary alkylcarbonyl groups include, but are not limited to, acetyl, propanoyl, isopropanoyl, butanoyl, etc.

The term "alkynyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond. Exemplary alkynyl groups include, but are not limited to, straight or branched groups of 2-6, or 3-6 carbon atoms, referred to herein as C_{2-6}alkynyl, and C_{3-6}alkynyl, respectively. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, etc.

The term "carbonyl" as used herein refers to the radical —C(O)—.

The term "cyano" as used herein refers to the radical —CN.

The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to oxygen (cycloalkyl-O—). Exemplary cycloalkoxy groups include, but are not limited to, cycloalkoxy groups of 3-6 carbon atoms, referred to herein as C_{3-6}cycloalkoxy groups. Exemplary cycloalkoxy groups include, but are not limited to, cyclopropoxy, cyclobutoxy, cyclohexyloxy, etc

The terms "cycloalkyl" or a "carbocyclic group" as used herein refers to a saturated or partially unsaturated hydrocarbon group of, for example, 3-6, or 4-6 carbons, referred to herein as C_{3-6}cycloalkyl or C_{4-6}cycloalkyl, respectively. Exemplary cycloalkyl groups include, but are not limited to, cyclohexyl, cyclopentyl, cyclopentenyl, cyclobutyl or cyclopropyl.

The terms "halo" or "halogen" as used herein refer to F, Cl, Br, or I.

The terms "heteroaryl" or "heteroaromatic group" as used herein refers to a monocyclic aromatic 5-6 membered ring system containing one or more heteroatoms, for example one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Where possible, said heteroaryl ring may be linked to the adjacent radical though carbon or nitrogen. Examples of heteroaryl rings include but are not limited to furan, thiophene, pyrrole, thiazole, oxazole, isothiazole, isoxazole, imidazole, pyrazole, triazole, pyridine or pyrimidine etc.

The terms "heterocyclyl" or "heterocyclic group" are art-recognized and refer to saturated or partially unsaturated, 4-10 membered ring structures, including bridged or fused rings, and whose ring structures include one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Where possible, heterocyclyl rings may be linked to the adjacent radical through carbon or nitrogen. Examples of heterocyclyl groups include, but are not limited to, pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, oxetane, azetidine, tetrahydrofuran or dihydrofuran etc.

The term "heterocyclyloxy" as used herein refers to a heterocyclyl group attached to oxygen (heterocyclyl-O—).

The term "heteroaryloxy" as used herein refers to a heteroaryl group attached to oxygen (heteroaryl-O—).

The terms "hydroxy" and "hydroxyl" as used herein refers to the radical —OH.

The term "oxo" as used herein refers to the radical =O.

"Pharmaceutically or pharmacologically acceptable" include molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, and general safety and purity standards as required by FDA Office of Biologics standards.

The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

The term "pharmaceutical composition" as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers.

"Individual," "patient," or "subject" are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. The compounds of the invention can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, e.g., domestic animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like). The mammal treated in the methods of the invention is desirably a mammal in which treatment of obesity or weight loss is

desired. "Modulation" includes antagonism (e.g., inhibition), agonism, partial antagonism and/or partial agonism.

In the present specification, the term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system or animal, (e.g. mammal or human) that is being sought by the researcher, veterinarian, medical doctor or other clinician. The compounds of the invention are administered in therapeutically effective amounts to treat a disease. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in weight loss.

The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in compounds used in the compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including, but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts, particularly calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

The compounds of the disclosure may contain one or more chiral centers and, therefore, exist as stereoisomers. The term "stereoisomers" when used herein consist of all enantiomers or diastereomers. These compounds may be designated by the symbols "(+)," "(−)," "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

The compounds of the disclosure may contain one or more double bonds and, therefore, exist as geometric isomers resulting from the arrangement of substituents around a carbon-carbon double bond. The symbol denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the "Z" or "E" configuration wherein the terms "Z" and "E" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "E" and "Z" isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond.

Compounds of the disclosure may contain a carbocyclic or heterocyclic ring and therefore, exist as geometric isomers resulting from the arrangement of substituents around the ring. The arrangement of substituents around a carbocyclic or heterocyclic ring are designated as being in the "Z" or "E" configuration wherein the terms "Z" and "E" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting carbocyclic or heterocyclic rings encompass both "Z" and "E" isomers. Substituents around a carbocyclic or heterocyclic rings may also be referred to as "cis" or "trans", where the term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

Individual enantiomers and diasteriomers of compounds of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well known methods, such as chiral-phase liquid chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations, and may involve the use of chiral auxiliaries. For examples, see Carreira and Kvaemo, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. In one embodiment, the compound is amorphous. In one embodiment, the compound is a single polymorph. In another embodiment, the compound is a mixture of polymorphs. In another embodiment, the compound is in a crystalline form.

The invention also embraces isotopically labeled compounds of the invention which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. For example, a compound of the invention may have one or more H atom replaced with deuterium.

Certain isotopically-labeled disclosed compounds (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or

substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in the examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

The term "prodrug" refers to compounds that are transformed in vivo to yield a disclosed compound or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (such as by esterase, amidase, phosphatase, oxidative and or reductive metabolism) in various locations (such as in the intestinal lumen or upon transit of the intestine, blood or liver). Prodrugs are well known in the art (for example, see Rautio, Kumpulainen, et al, Nature Reviews Drug Discovery 2008, 7, 255). For example, if a compound of the invention or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_{1-8})alkyl, (C_{2-12})alkylcarbonyloxymethyl, 1-(alkylcarbonyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkylcarbonyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl) amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N—(C_{1-2})alkylamino(C_{2-3})alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_{1-2})alkyl, N,N-di(C_{1-2})alkylcarbamoyl-(C_{1-2})alkyl and piperidino-, pyrrolidino- or morpholino (C_{2-3})alkyl.

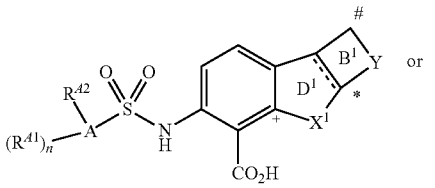
Similarly, if a compound of the invention contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_{1-6})alkylcarbonyloxymethyl, 1-((C_{1-6})alkylcarbonyloxy)ethyl, 1-methyl-1-((C_{1-6})alkylcarbonyloxy)ethyl (C_{1-6})alkoxycarbonyloxymethyl, N—(C_{1-6})alkoxycarbonylaminomethyl, succinoyl, (C_{1-6})alkylcarbonyl, α-amino (C_{1-4})alkylcarbonyl, arylalkylcarbonyl and α-aminoalkylcarbonyl, or α-aminoalkylcarbonyl-α-aminoalkylcarbonyl, where each α-aminoalkylcarbonyl group is independently selected from the naturally occurring L-amino acids, P(O)$(OH)_2$, —P(O)(O(C_{1-6})alkyl$)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

If a compound of the invention incorporates an amine functional group, a prodrug can be formed, for example, by creation of an amide or carbamate, an N-alkylcarbonyloxyalkyl derivative, an (oxodioxolenyl)methyl derivative, an N-Mannich base, imine or enamine. In addition, a secondary amine can be metabolically cleaved to generate a bioactive primary amine, or a tertiary amine can metabolically cleaved to generate a bioactive primary or secondary amine. For examples, see Simplicio, et al., *Molecules* 2008, 13, 519 and references therein.

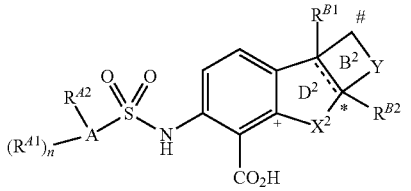
I. Tricyclic Compounds

In certain embodiments, the present invention provides compounds of Formula I or Formula II:

Formula I



Formula II



wherein

B^1 may be a 3-6 membered saturated or partially unsaturated heterocyclic or carbocyclic ring;

B^2 may be a 3-6 membered saturated heterocyclic or carbocyclic ring;

wherein the ring B^1 or B^2 may optionally be substituted by one or more fluorine atoms on any of the available carbon atoms

D^1 may be a 5-7 membered heterocyclic, carbocyclic, heteroaromatic or aromatic ring;

D^2 may be a 5-7 membered heterocyclic or carbocyclic ring;

wherein B^1 is fused to D^1 such that the two atoms shared by B^1 and D^1 are both carbon and B^2 is fused to D^2 such that the two atoms shared by B^2 and D^2 are both carbon; and wherein for Formula I the bond common to both the B^1 and D^1 rings may be a single or double bond;

X^1 may be selected from the group consisting of: $^{+}$—C$(R^{D1}R^{D2})$—*, $^{+}$—W^1—*, $^{+}$—C$(R^{D1}R^{D2})$—C$(R^{D5}R^{D6})$—*, $^{+}$—C(R^{C1})=C(R^{C2})—*, $^{+}$—W^2—C$(R^{D5}R^{D6})$—*, $^{+}$—W^2—C(O)—*, $^{+}$—C$(R^{D1}R^{D2})$—W^4—*, $^{+}$—N=C(R^{C2})—*, $^{+}$—C(R^{C1})=N—*, $^{+}$—C$(R^{D1}R^{D2})$—C$(R^{D3}R^{D4})$—C$(R^{D5}R^{D6})$—*, $^{+}$—W^2—C$(R^{D3}R^{D4})$—C$(R^{D5}R^{D6})$—*, $^{+}$—W^2—C(O)—C$(R^{D5}R^{D6})$—*, $^{+}$—C$(R^{D1}R^{D2})$—W^3—C$(R^{D5}R^{D6})$—*, $^{+}$—C$(R^{D1}R^{D2})$—W^3—C(O)—*, $^{+}$—C$(R^{D1}R^{D2})$—C$(R^{D3}R^{D4})$—W^4—* and $^{+}$—C$(R^{D1}R^{D2})$—C(O)—W^4—*; wherein the $^{+}$ and * indicate the attachment points of X^1 as indicated in Formula I;

X^2 may be selected from the group consisting of: $^{+}$—C$(R^{D1}R^{D2})$—*, $^{+}$—W^1—*, $^{+}$—C$(R^{D1}R^{D2})$—C$(R^{D5}R^{D6})$—*, $^{+}$—W^2—C$(R^{D5}R^{D6})$—*, $^{+}$—W^2—C(O)—*, $^{+}$—C$(R^{D1}R^{D2})$—W^4—*, $^{+}$—C$(R^{D1}R^{D2})$—C$(R^{D3}R^{D4})$—C$(R^{D5}R^{D6})$—*, $^{+}$—W^2—C$(R^{D3}R^{D4})$—C$(R^{D5}R^{D6})$—*, $^{+}$—W^2—C(O)—C$(R^{D5}R^{D6})$—*, $^{+}$—C$(R^{D1}R^{D2})$—W^3—C$(R^{D5}R^{D6})$—*, $^{+}$—C$(R^{D1}R^{D2})$—W^3—C(O)—*, $^{+}$—C$(R^{D1}R^{D2})$—C$(R^{D3}R^{D4})$—W^4—* and $^{+}$—C$(R^{D1}R^{D2})$—C(O)—W^4—*; wherein the $^{+}$ and * indicate the attachment points of X^2 as indicated in Formula II;

Y may be selected from the group consisting of: a bond, *—CH_2—$^{\#}$, *—O—$^{\#}$, *—CH_2—CH_2—$^{\#}$, *—O—CH_2—$^{\#}$, *—CH_2—O—$^{\#}$, *—CH_2—CH_2—CH_2—$^{\#}$, *—O—CH_2—CH_2—$^{\#}$ and *—CH_2—O—CH_2—$^{\#}$; wherein the * and $^{\#}$ indicate the attachment points of Y as indicated in Formula I or Formula II;

W^1 may be selected from the group consisting of O, S, or $N(R^{N1})$;

W^2 may be selected from the group consisting of O or $N(R^{N2})$;

W^3 may be selected from the group consisting of O or $N(R^{N3})$;

W^4 may be selected from the group consisting of O or $N(R^{N4})$;

A may be a ring selected from the group consisting of phenyl, a 5-6 membered heteroaryl having 1, 2 or 3 heteroatoms each selected from S, N or O, and a 4-7 membered heterocycle having 1, 2 or 3 heteroatoms each selected from N or O;

R^{B1} and R^{B2} are independently selected from the group consisting of H, F, OH, CN, C_{1-2}alkoxy or C_{1-3}alkyl; wherein C_{1-3}alkyl and C_{1-2}alkoxy are optionally substituted by a group selected from OH, C_{1-2}alkoxy, CN or one or more fluorine atoms;

R^{A1} may be selected, independently for each occurrence, from the group consisting of hydrogen, hydroxyl, cyano, halogen, C_{1-4}alkyl or C_{1-3}alkoxy; wherein C_{1-4}alkyl, or C_{1-3}alkoxy may be optionally substituted by one or more fluorines;

n may be 1 or 2;

R^{A2} may be selected from the group consisting of hydrogen, R^iR^jN—, heterocyclyl, heterocyclyloxy and heterocyclyl-(NR^a)—; wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g and wherein if said heterocyclyl contains a —NH moiety that nitrogen may optionally be substituted by one or more groups R^h; or

R^{A2} may be selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl-$S(O)_w$— (wherein w is 0, 1 or 2), C_{1-6}alkyl-$N(R^a)$—, C_{1-6}alkyl-$N(R^a)$-carbonyl-, C_{1-6}alkyl-carbonyl-$N(R^a)$—, C_{1-6}alkyl-$N(R^a)$-carbonyl-$N(R^a)$—, C_{1-6}alkyl-$N(R^a)$—SO_2—, C_{1-6}alkyl-SO_2—$N(R^a)$—, C_{1-6}alkoxycarbonyl-$N(R^a)$—, C_{1-6}alkylcarbonyl-$N(R^a)$—C_{1-6}alkyl-, C_{1-6}alkyl-$N(R^a)$-carbonyl-C_{1-6}alkyl-, C_{1-6}alkoxyC_{1-6}alkyl-; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl-$S(O)_w$—, C_{1-6}alkyl-$N(R^a)$—, C_{1-6}alkyl-$N(R^a)$-carbonyl-, C_{1-6}alkyl-carbonyl-$N(R^a)$—, C_{1-6}alkyl-$N(R^a)$-carbonyl-$N(R^a)$—, C_{1-6}alkyl-$N(R^a)$—SO_2—, C_{1-6}alkyl-SO_2—$N(R^a)$—, C_{1-6}alkoxycarbonyl-$N(R^a)$—, C_{1-6}alkylcarbonyl-$N(R^a)$ C_{1-6}alkyl-, C_{1-6}alkyl-$N(R^a)$-carbonyl-C_{1-6}alkyl-, C_{1-6}alkoxy-C_{1-6}alkyl may optionally be substituted by R^P, phenyl, phenoxy, heteroaryl, heteroaryloxy, heteroaryl-(NR^a)—, heterocyclyl, heterocyclyloxy or heterocyclyl-$N(R^a)$—; and wherein said heteroaryl or phenyl may optionally be substituted with one or more substituents selected from R^f; and wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g; and wherein if said heterocyclyl contains a —NH moiety that nitrogen may optionally be substituted by one or more groups R^h;

R^{D1} and R^{D2} may be each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano or hydroxyl;

R^{D3} and R^{D4} may be each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-3}alkyl or C_{1-3}alkoxy; wherein the C_{1-3} alkyl and C_{1-3} alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{D5} and R^{D6} may be each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{C1} may be selected from the group consisting of hydrogen, halogen, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl or C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms;

R^{C2} may be selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{N1} may be selected from the group consisting of hydrogen or C_{1-2}alkyl;

R^{N2} may be selected from the group consisting of hydrogen or C_{1-2}alkyl;

R^{N3} may be selected from the group consisting of hydrogen, C_{1-3}alkyl or C_{1-2}alkylcarbonyl; wherein the C_{1-3}alkyl and C_{1-2}alkylcarbonyl may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{N4} may be selected from the group consisting of hydrogen, C_{1-3}alkyl or C_{1-2}alkylcarbonyl; wherein the C_{1-3}alkyl and C_{1-2}alkylcarbonyl may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^a and R^b may be independently selected, for each occurrence, from the group consisting of hydrogen and C_{1-3}alkyl; wherein C_{1-3}alkyl may optionally be substituted by one or more substituents selected from fluorine, cyano, oxo and hydroxyl;

or R^a and R^b, together with the nitrogen to which they are attached, may form a 4-6 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-6 membered heterocyclic ring may optionally be substituted by one or more substituents selected from the group consisting of fluorine, cyano, oxo or hydroxyl;

R^f may be independently selected, for each occurrence, from the group consisting of R^P, hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, (wherein w is 0, 1 or 2), C_{1-6}alkylcarbonyl-$N(R^a)$— and C_{1-6}alkoxycarbonyl-$N(R^a)$—; wherein C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, C_{1-6}alkylcarbonyl-$N(R^a)$—, C_{1-6}alkoxycarbonyl-$N(R^a)$— may be optionally substituted by one or more substituents selected from R^P;

R^g may be independently selected for each occurrence from the group consisting of R^P, hydrogen, oxo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, (wherein w is 0, 1 or 2), C_{1-6}alkylcarbonyl-$N(R^a)$— and C_{1-6}alkoxycarbonyl-$N(R^a)$—; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, C_{1-6}alkylcarbonyl-$N(R^a)$—, C_{1-6}alkoxycarbonyl-$N(R^a)$— may be optionally substituted by one or more substituents selected from R^P;

R^h may be independently selected for each occurrence from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$—, C_{1-6}alkoxycarbonyl-, R^iR^jN-carbonyl- and R^iR^jN—SO_2—; wherein C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl C_{3-6}cycloalkyl and C_{1-6}alkyl-$S(O)_2$—, C_{1-6}alkylcarbonyl- may optionally be substituted by one or more substituents selected from R^P;

R^i and R^j may be selected independently for each occurrence from the group consisting of hydrogen, C_{1-4}alkyl

C_{3-6}cycloalkyl, heterocyclyl and heterocyclylcarbonyl; wherein C_{1-4}alkyl and C_{3-6}cycloalkyl may be optionally substituted by one or more substituents selected from fluorine, hydroxyl, cyano, R^aR^bN—, R^aR^bN-carbonyl- and C_{1-3}alkoxy and wherein heterocyclyl and heterocyclylcarbonyl may be optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, halo-C_{1-6}-alkyl, hydroxyl-C_{1-6}-alkyl, R^aR^bN—C_{1-6}alkyl- and C_{1-6}-alkoxy-C_{1-6}-alkyl group; and wherein if said heterocyclyl or heterocyclylcarbonyl contains a —NH moiety that nitrogen may optionally be substituted by one or more groups C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$— and C_{1-6}-alkylcarbonyl;

or R^i and R^j taken together with the nitrogen to which they are attached may form a 4-7 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-7 membered heterocyclic ring may be optionally substituted on carbon by one or more substituents selected from the group consisting of fluorine, hydroxyl, oxo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, R^aR^bN—, R^aR^bN—SO_2— and R^aR^bN-carbonyl-; wherein said C_{1-6}alkyl or C_{1-6}alkoxy may optionally be substituted by fluorine, hydroxyl or cyano; and wherein the 4-7 membered heterocyclic ring may be optionally substituted on nitrogen by one or more substituents selected from the group consisting of C_{1-6}alkyl and R^aR^bN-carbonyl-; and wherein said C_{1-6}alkyl may be optionally substituted by fluorine, hydroxyl, cyano;

R^P may be independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, cyano, C_{1-6}alkoxy, R^iR^jN—, R^iR^jN-carbonyl-, R^iR^jN—SO_2— and R^iR^jN-carbonyl-$N(R^a)$—;

and pharmaceutically acceptable salts, stereoisomers, esters and prodrugs thereof.

In some embodiments, X^1 may be selected from the group consisting of: $^+$—O—*, $^+$—$N(R^{N1})$—*, $^+$—$C(R^{D1}R^{D2})$—$C(R^{D5}R^{D6})$—*, $^+$—$C(R^{C1})$=$C(R^{C2})$—*, $^+$—O—$C(R^{D5}R^{D6})$—*, $^+$—$N(R^{N2})$—$C(R^{D5}R^{D6})$—*, $^+$—O—C(O)—*, $^+$—$N(R^{N2})$—C(O)—*, $^+$—N=$C(R^{C2})$—* and $^+$—O—$C(R^{D3}R^{D4})$—$C(R^{D5}R^{D6})$—*; wherein the $^+$ and * indicate the attachment points of X^1 as indicated in Formula I. Exemplary X^1 moities may be selected from the group consisting of: $^+$—NH—*, $^+$—O—CH_2—*, $^+$—NH—CH_2—*, $^+$—N=CH—* and $^+$—CH=CH—*; wherein the $^+$ and * indicate the attachment points of X^1 as indicated in Formula I.

In some embodiments X^2 may be selected from the group consisting of $^+$—O—*, $^+$—$N(R^{N1})$—*, $^+$—$C(R^{D1}R^{D2})$—$C(R^{D5}R^{D6})$—*, $^+$—O—$C(R^{D5}R^{D6})$—*, $^+$—$N(R^{N2})$—$C(R^{D5}R^{D6})$—*, $^+$—O—C(O)—*, $^+$—$N(R^{N2})$—C(O)—*, and $^+$—O—$C(R^{D3}R^{D4})$—$C(R^{D5}R^{D6})$—*; wherein the $^+$ and * indicate the attachment points of X^2 as indicated in Formula II. Exemplary X^2 moities may be selected from the group consisting of: $^+$—O—CH_2—* and $^+$—NH—CH_2—*; wherein the $^+$ and * indicate the attachment points of X^2 as indicated in Formula II.

In one embodiment, R^{D1}, R^{D2}, R^{C1}, R^{N1} and R^{N2} may be independently selected for each occurrence from the group consisting of hydrogen and methyl. For example, R^{D1}, R^{D2}, R^{C1}, R^{N1} and R^{N2} may be hydrogen.

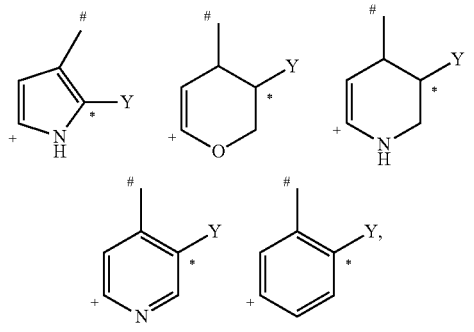
In certain embodiments, R^{D3}, R^{D4}, R^{D5} and R^{D6} may be independently selected for each occurrence from the group consisting of hydrogen, fluorine, cyano and C_{1-2}alkyl. For example, R^{D3}, R^{D4}, R^{D5} and R^{D6} may be hydrogen.

In an embodiment, R^{C2} may be selected from the group consisting of hydrogen, halogen, cyano and C_{1-2}alkyl. For example, R^{C2} may be hydrogen.

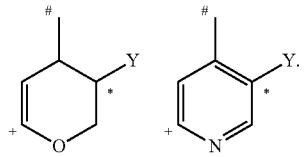
In certain embodiments, R^{B1} of the tricyclic compound of Formula II may be selected from the group consisting of H, F or C_{1-2}alkyl. For example, R^{B1} may be H or methyl.

In another embodiment, R^{B2} of the tricyclic compound of Formula II may be hydrogen.

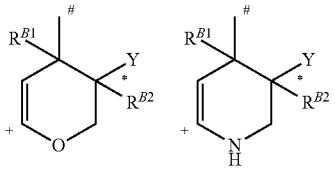
In certain embodiments, ring D^1 may be selected from the group consisting of:



wherein the *, # and + indicate the points of attachment to the phenyl ring and the B^1 ring as indicated in Formula I. Exemplary D^1 rings that may form part of the contemplated tricyclic core may include those selected from the group consisting of:



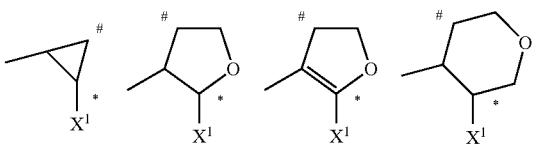
In certain embodiments, ring D^2 may be selected from the group consisting of:



wherein the *, # and + indicate the points of attachment to the phenyl ring and the B^2 ring as indicated in Formula II.

In some embodiments, Y may be selected from the group consisting of a bond, *—O—CH_2—# and *—CH_2—O—CH_2—#; wherein the * and # indicate the points of attachment to Y as indicated in Formula I or Formula II. For example, Y may be a bond or *—O—CH_2—#; wherein the * and # indicate the points of attachment to Y as indicated in Formula I or Formula II.

For example, ring B^1 or B^2 may, in certain embodiments, be selected from the group consisting of:



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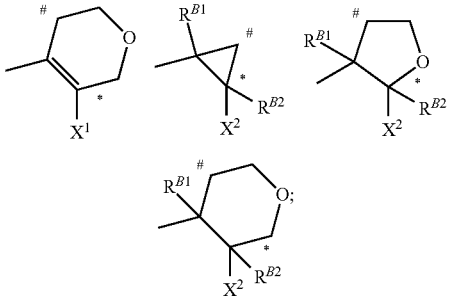
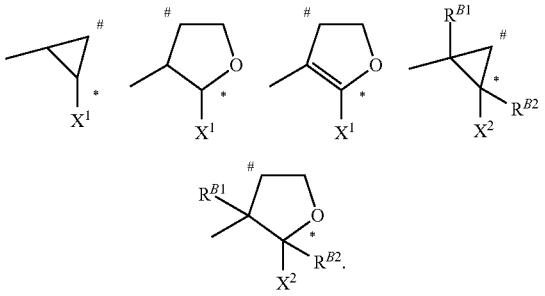
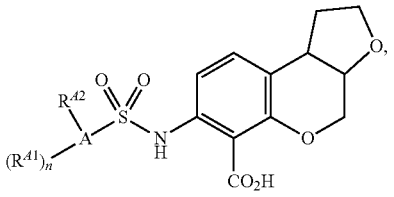


wherein the * and # indicate the points of attachment to Y as indicated in Formula I and II. Exemplary B^1 and B^2 rings that may form part of the contemplated tricyclic core may include those selected from the group consisting of:

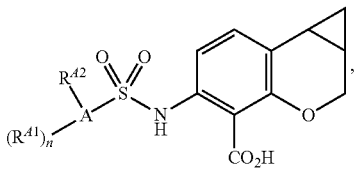


Provided herein, for example, are tricyclic compounds represented by formulas Ia, Ib, Ic, Id, Ie, If and Ig:

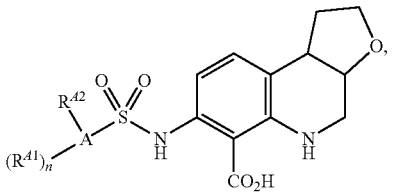
Ia



Ib



Ic



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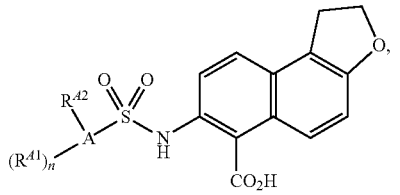
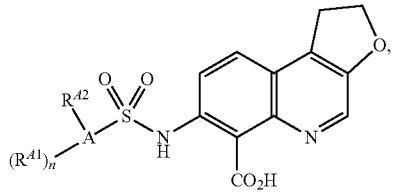
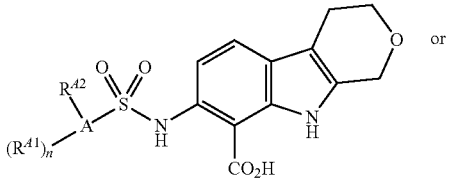
Id



Ie

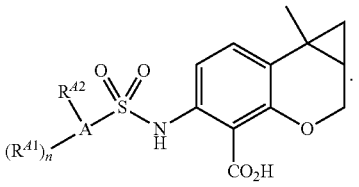


If



or

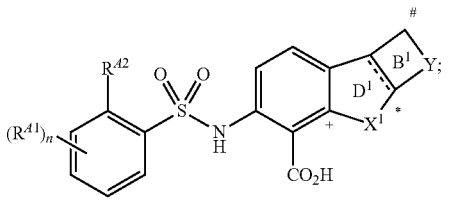
Ig



In certain embodiments, A may be phenyl.

Also provided herein is a compound represented by Formula III:

Formula III



wherein:

B^1 may be a 3-6 membered saturated or partially unsaturated heterocyclic or carbocyclic ring; wherein the ring B^1 may optionally be substituted by one or more fluorine atoms on any of the available carbon atoms;

D^1 may be a 5-7 membered heterocyclic, carbocyclic, heteroaromatic or aromatic ring; wherein B^1 is fused to D^1 such that the two atoms shared by B^1 and D^1 are both carbon; and wherein the bond common to both the B^1 and D^1 rings may be a single or double bond;

X^1 may be selected from the group consisting of: $^+$—C($R^{D1}R^{D2}$)—*, $^+$—W^1*, $^+$—C($R^{D1}R^{D2}$)—C($R^{D5}R^{D6}$)—*, $^+$—C(R^{C1})=C(R^{C2})—*, $^+$—W^2—C($R^{D5}R^{D6}$)—*, $^+$—W^2—C(O)—*, $^+$—C($R^{D1}R^{D2}$)—W^4—*, $^+$—N=C(R^{C2})—*, $^+$—C(R^{C1})=N—*, $^+$—C($R^{D1}R^{D2}$)—C($R^{D3}R^{D4}$)—C($R^{D5}R^{D6}$*, $^+$—W^2—C($R^{D3}R^{D4}$)—C($R^{D5}R^{D6}$)—*, $^+$—W^2—C(O)—C($R^{D5}R^{D6}$)—*, $^+$—C

$(R^{D1}R^{D2})$—W^3—$C(R^{D5}R^{D6})$—*, $^+$—$C(R^{D1}R^{D2})$—W^3—C(O)—*, $^+$—$C(R^{D1}R^{D2})$—$C(R^{D3}R^{D4})$—W^4—* and $^+$—$C(R^{D1}R^{D2})$—C(O)—W^4—*; wherein the $^+$ and * indicate the attachment points of X^1 as indicated in Formula III;

Y may be selected from the group consisting of: a bond, *—CH_2—$^{\#}$, *—O—$^{\#}$, *—CH_2—CH_2—$^{\#}$, *—O—CH_2—$^{\#}$, *—CH_2—O—$^{\#}$, *—CH_2—CH_2—CH_2—$^{\#}$, *—O—CH_2—CH_2—$^{\#}$ and *—CH_2—O—CH_2—$^{\#}$; wherein the * and $^{\#}$ indicate the attachment points of Y as indicated in Formula III;

W^1 may be selected from the group consisting of O, S or $N(R^{N1})$;

W^2 may be selected from the group consisting of O or $N(R^{N2})$;

W^3 may be selected from the group consisting of O or $N(R^{N3})$;

W^4 may be selected from the group consisting of O or $N(R^{N4})$;

R^{A1} may be selected, independently for each occurrence, from the group consisting of hydrogen, hydroxyl, cyano, halogen, C_{1-4}alkyl or C_{1-3}alkoxy; wherein C_{1-4}alkyl, or C_{1-3}alkoxy may be optionally substituted by one or more fluorines;

n may be 0, 1, or 2;

R^{A2} may be selected from the group consisting of hydrogen, R^iR^jN—, heterocyclyl, heterocyclyloxy and heterocyclyl-(NR^a)—; wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g and wherein if said heterocyclyl contains a —NH moiety that nitrogen may optionally be substituted by one or more groups R^h; or

R^{A2} may be selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl-$S(O)_w$— (wherein w is 0, 1 or 2), C_{1-6}alkyl-$N(R^a)$—, C_{1-6}alkyl-$N(R^a)$-carbonyl-, C_{1-6}alkyl-carbonyl-$N(R^a)$—, C_{1-6}alkyl-$N(R^a)$-carbonyl-$N(R^a)$—, C_{1-6}alkyl-$N(R^a)$—SO_2—, C_{1-6}alkyl-SO_2—$N(R^a)$—, C_{1-6}alkoxycarbonyl-$N(R^a)$—, C_{1-6}alkylcarbonyl-$N(R^a)$—C_{1-6}alkyl-, C_{1-6}alkyl-$N(R^a)$-carbonyl-C_{1-6}alkyl-, C_{1-6}alkoxyC_{1-6}alkyl-; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl-$S(O)_w$—, C_{1-6}alkyl-$N(R^a)$—, C_{1-6}alkyl-$N(R^a)$-carbonyl-, C_{1-6}alkyl-carbonyl-$N(R^a)$—, C_{1-6}alkyl-$N(R^a)$-carbonyl-$N(R^a)$—, C_{1-6}alkyl-$N(R^a)$—SO_2—, C_{1-6}alkyl-SO_2—$N(R^a)$—, C_{1-6}alkoxycarbonyl-$N(R^a)$—, C_{1-6}alkylcarbonyl-$N(R^a)$ C_{1-6}alkyl-, C_{1-6}alkyl-$N(R^a)$-carbonyl-C_{1-6}alkyl-, C_{1-6}alkoxy-C_{1-6}alkyl may optionally be substituted by R^P, phenyl, phenoxy, heteroaryl, heteroaryloxy, heteroaryl-(NR^a)—, heterocyclyl, heterocyclyloxy or heterocyclyl-N(R^a)—; and wherein said heteroaryl or phenyl may optionally be substituted with one or more substituents selected from R^f; and wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g; and wherein if said heterocyclyl contains a —NH moiety that nitrogen may optionally be substituted by one or more groups R^h;

R^{D1} and R^{D2} may be each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano or hydroxyl;

R^{D3} and R^{D4} may be each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-3}alkyl or C_{1-3}alkoxy; wherein the C_{1-3} alkyl and C_{1-3} alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{D5} and R^{D6} may be each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{C1} may be selected from the group consisting of hydrogen, halogen, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl or C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms;

R^{C2} may be selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{N1} may be selected from the group consisting of hydrogen or C_{1-2}alkyl;

R^{N2} may be selected from the group consisting of hydrogen or C_{1-2}alkyl;

R^{N3} may be selected from the group consisting of hydrogen, C_{1-3}alkyl or C_{1-2}alkylcarbonyl; wherein the C_{1-3}alkyl and C_{1-2}alkylcarbonyl may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{N4} may be selected from the group consisting of hydrogen, C_{1-3}alkyl or C_{1-2}alkylcarbonyl; wherein the C_{1-3}alkyl and C_{1-2}alkylcarbonyl may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^a and R^b may be independently selected, for each occurrence, from the group consisting of hydrogen and C_{1-3}alkyl; wherein C_{1-3}alkyl may optionally be substituted by one or more substituents selected from fluorine, cyano, oxo and hydroxyl;

or R^a and R^b, together with the nitrogen to which they are attached, may form a 4-6 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-6 membered heterocyclic ring may optionally be substituted by one or more substituents selected from the group consisting of fluorine, cyano, oxo or hydroxyl;

R^f may be independently selected, for each occurrence, from the group consisting of R^P, hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, (wherein w is 0, 1 or 2), C_{1-6}alkylcarbonyl-$N(R^a)$— and C_{1-6}alkoxycarbonyl-$N(R^a)$—; wherein C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, C_{1-6}alkylcarbonyl-$N(R^a)$—, C_{1-6}alkoxycarbonyl-$N(R^a)$— may be optionally substituted by one or more substituents selected from R^P;

R^g may be independently selected for each occurrence from the group consisting of R^P, hydrogen, oxo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, (wherein w is 0, 1 or 2), C_{1-6}alkylcarbonyl-$N(R^a)$— and C_{1-6}alkoxycarbonyl-$N(R^a)$—; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, C_{1-6}alkylcarbonyl-$N(R^a)$—, C_{1-6}alkoxycarbonyl-$N(R^a)$— may be optionally substituted by one or more substituents selected from R^P;

R^h may be independently selected for each occurrence from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$—, C_{1-6}alkoxycarbonyl-, R^iR^jN-carbonyl- and R^iR^jN—SO_2—; wherein C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl C_{3-6}cycloalkyl and C_{1-6}alkyl-$S(O)_2$—, C_{1-6}alkylcarbonyl- may optionally be substituted by one or more substituents selected from R^P;

R^i and R^j may be selected independently for each occurrence from the group consisting of hydrogen, C_{1-4}alkyl

C_{3-6}cycloalkyl, heterocyclyl and heterocyclylcarbonyl; wherein C_{1-4}alkyl and C_{3-6}cycloalkyl may be optionally substituted by one or more substituents selected from fluorine, hydroxyl, cyano, R^aR^bN—, R^aR^bN-carbonyl- and C_{1-3}alkoxy and wherein heterocyclyl and heterocyclylcarbonyl may be optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, halo-C_{1-6}-alkyl, hydroxyl-C_{1-6}-alkyl, R^aR^bN—C_{1-6}alkyl- and C_{1-6}-alkoxy-C_{1-6}-alkyl group; and wherein if said heterocyclyl or heterocyclylcarbonyl contains a —NH moiety that nitrogen may optionally be substituted by one or more groups C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$— and C_{1-6}-alkylcarbonyl;

or R^i and R^j taken together with the nitrogen to which they are attached may form a 4-7 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-7 membered heterocyclic ring may be optionally substituted on carbon by one or more substituents selected from the group consisting of fluorine, hydroxyl, oxo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, R^aR^bN—, R^aR^bN—SO_2— and R^aR^bN-carbonyl-; wherein said C_{1-6}alkyl or C_{1-6}alkoxy may optionally be substituted by fluorine, hydroxyl or cyano; and wherein the 4-7 membered heterocyclic ring may be optionally substituted on nitrogen by one or more substituents selected from the group consisting of C_{1-6}alkyl and R^aR^bN-carbonyl-; and wherein said C_{1-6}alkyl may be optionally substituted by fluorine, hydroxyl, cyano;

R^P may be independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, cyano, C_{1-6}alkoxy, R^iR^jN—, R^iR^jN-carbonyl-, R^iR^jN—SO_2— and R^iR^jN-carbonyl-N(R^a)—;

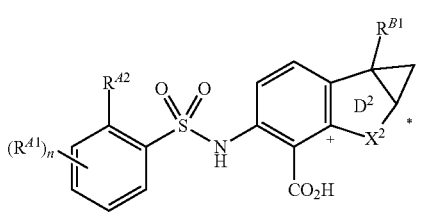
and pharmaceutically acceptable salts, stereoisomers, esters and prodrugs thereof.

In certain embodiments, R^{A1} of the tricyclic compound of Formula III may be selected from the group consisting of hydrogen, halogen, C_{1-2}alkyl and C_{1-2}alkoxy; wherein C_{1-2}alkyl may optionally be substituted by one or more fluorines. For example, R^{A1} may be hydrogen or fluorine.

In another embodiment, R^{A2} of the tricyclic compound of Formula III may be selected from the group consisting of hydrogen, R^iR^jN, heterocyclyl, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy; wherein said heterocyclyl may optionally be substituted by one or more groups R^g; and wherein if said heterocyclyl contains a —NH moiety, that nitrogen may optionally be substituted by on or more groups R^h; and wherein said C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}cycloalkyl and C_{1-6}alkoxy may optionally be substituted by one or more groups R^P. For example, R^{A2} may be selected from the group consisting of 3-(N,N-diethylamino)propyl, 3-(pyrrolidin-1-yl)propyl, (Z)-3-(N,N-diethylamino)prop-1-enyl, (Z)-3-(azetidin-1-yl)prop-1-enyl and (Z)-3-(pyrrolidin-1-yl)prop-1-enyl.

Also provided herein is a compound represented by Formula IV:

Formula IV



D^2 may be a 5-7 membered partially unsaturated heterocyclic or carbocyclic ring;

X^2 may be selected from the group consisting of: $^+$—C($R^{D1}R^{D2}$)—*, $^+$—W^1—*$^+$—C($R^{D1}R^{D2}$)—C($R^{D5}R^{D6}$)—*, $^+$—W^2—C($R^{D5}R^{D6}$)—*, $^+$—W^2—C(O)—*, $^+$—C($R^{D1}R^{D2}$)—W^4—*, $^+$—C($R^{D1}R^{D2}$)—C($R^{D3}R^{D4}$)—C($R^{D5}R^{D6}$)—*, $^+$—W^2—C($R^{D3}R^{D4}$)—C($R^{D5}R^{D6}$)—*, $^+$—W^2—C(O)—C($R^{D5}R^{D6}$)—*, +C($R^{D1}R^{D2}$)—W^3—C($R^{D5}R^{D6}$)—*, $^+$—C($R^{D1}R^{D2}$)—W^3—C(O)—*, $^+$—C($R^{D1}R^{D2}$)—C($R^{D3}R^{D4}$)—W^4—* and $^+$—C($R^{D1}R^{D2}$)—C(O)—W^4—*; wherein the $^+$ and * indicate the attachment points of X^2 as indicated in Formula IV;

W^1 may be selected from the group consisting of O, S or N(R^{N1});

W^2 may be selected from the group consisting of O or N(R^{N2});

W^3 may be selected from the group consisting of O or N(R^{N3});

W^4 may be selected from the group consisting of O or N(R^{N4});

R^{B1} may be selected from the group consisting of H, F, OH, CN, C_{1-2}alkoxy or C_{1-3}alkyl; wherein C_{1-3}alkyl and C_{1-2}alkoxy are optionally substituted by a group selected from OH, C_{1-2}alkoxy, CN or one or more fluorine atoms;

R^{A1} may be selected, independently for each occurrence, from the group consisting of hydrogen, hydroxyl, cyano, halogen, C_{1-4}alkyl or C_{1-3}alkoxy; wherein C_{1-4}alkyl, or C_{1-3}alkoxy may be optionally substituted by one or more fluorines;

n may be 0, 1, or 2;

R^{A2} may be selected from the group consisting of hydrogen, R^iR^jN—, heterocyclyl, heterocyclyloxy and heterocyclyl-(NR^a)—; wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g and wherein if said heterocyclyl contains a —NH moiety that nitrogen may optionally be substituted by one or more groups R^h; or

R^{A2} may be selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl-$S(O)_w$— (wherein w is 0, 1 or 2), C_{1-6}alkyl-N(R^a)—, C_{1-6}alkyl-N(R^a)-carbonyl-, C_{1-6}alkyl-carbonyl-N(R^a)—, C_{1-6}alkyl-N(R^a)-carbonyl-N(R^a)—, C_{1-6}alkyl-N(R^a)—SO_2—, C_{1-6}alkyl-SO_2—N(R^a)—, C_{1-6}alkoxycarbonyl-N(R^a)—, C_{1-6}alkylcarbonyl-N(R^a)—C_{1-6}alkyl-, C_{1-6}alkyl-N(R^a)-carbonyl-C_{1-6}alkyl-, C_{1-6}alkoxyC_{1-6}alkyl-; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl-$S(O)_w$—, C_{1-6}alkyl-N(R^a)—, C_{1-6}alkyl-N(R^a)-carbonyl-, C_{1-6}alkyl-carbonyl-N(R^a)—, C_{1-6}alkyl-N(R^a)-carbonyl-N(R^a)—, C_{1-6}alkyl-N(R^a)—SO_2—, C_{1-6}alkyl-SO_2—N(R^a)—, C_{1-6}alkoxycarbonyl-N(R^a)—, C_{1-6}alkylcarbonyl-N(R^a)C_{1-6}alkyl-, C_{1-6}alkyl-N(R^a)-carbonyl-C_{1-6}alkyl-, C_{1-6}alkoxy-C_{1-6}alkyl may optionally be substituted by R^P, phenyl, phenoxy, heteroaryl, heteroaryloxy, heteroaryl-(NR^a)—, heterocyclyl, heterocyclyloxy or heterocyclyl-N(R^a)—; and wherein said heteroaryl or phenyl may optionally be substituted with one or more substituents selected from R^f; and wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g; and wherein if said heterocyclyl contains a —NH moiety that nitrogen may optionally be substituted by one or more groups R^h;

R^{D1} and R^{D2} may be each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may

optionally be substituted by one or more fluorine atoms or a group selected from cyano or hydroxyl;

R^{D3} and R^{D4} may be each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-3}alkyl or C_{1-3}alkoxy; wherein the C_{1-3} alkyl and C_{1-3} alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{D5} and R^{D6} may be each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorine atoms, cyano, hydroxyl or $N(R^aR^b)$;

R^{C1} may be selected from the group consisting of hydrogen, halogen, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl or C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms;

R^{C2} may be selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{N1} may be selected from the group consisting of hydrogen or C_{1-2}alkyl;

R^{N2} may be selected from the group consisting of hydrogen or C_{1-2}alkyl;

R^{N3} may be selected from the group consisting of hydrogen, C_{1-3}alkyl or C_{1-2}alkylcarbonyl; wherein the C_{1-3}alkyl and C_{1-2}alkylcarbonyl may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorines, cyano, hydroxyl or $N(R^aR^b)$;

R^{N4} may be selected from the group consisting of hydrogen, C_{1-3}alkyl or C_{1-2}alkylcarbonyl; wherein the C_{1-3}alkyl and C_{1-2}alkylcarbonyl may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorines, cyano, hydroxyl or $N(R^aR^b)$;

R^a and R^b may be independently selected, for each occurrence, from the group consisting of hydrogen and C_{1-3}alkyl; wherein C_{1-3}alkyl may optionally be substituted by one or more substituents selected from fluorine, cyano, oxo and hydroxyl;

or R^a and R^b, together with the nitrogen to which they are attached, may form a 4-6 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-6 membered heterocyclic ring may optionally be substituted by one or more substituents selected from the group consisting of fluorine, cyano, oxo or hydroxyl;

R^f may be independently selected, for each occurrence, from the group consisting of R^P, hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, (wherein w is 0, 1 or 2), C_{1-6}alkylcarbonyl-$N(R^a)$— and C_{1-6}alkoxycarbonyl-$N(R^a)$—; wherein C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, C_{1-6}alkylcarbonyl-$N(R^a)$—, C_{1-6}alkoxycarbonyl-$N(R^a)$— may be optionally substituted by one or more substituents selected from R^P;

R^g may be independently selected for each occurrence from the group consisting of R^P, hydrogen, oxo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, (wherein w is 0, 1 or 2), C_{1-6}alkylcarbonyl-$N(R^a)$— and C_{1-6}alkoxycarbonyl-$N(R^a)$—; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, C_{1-6}alkylcarbonyl-$N(R^a)$—, C_{1-6}alkoxycarbonyl-$N(R^a)$— may be optionally substituted by one or more substituents selected from R^P;

R^h may be independently selected for each occurrence from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$—, C_{1-6}alkoxycarbonyl-, R^iR^jN-carbonyl- and R^iR^jN—SO_2—; wherein C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl C_{3-6}cycloalkyl and C_{1-6}alkyl-$S(O)_2$—, C_{1-6}alkylcarbonyl- may optionally be substituted by one or more substituents selected from R^P;

R^i and R^j may be selected independently for each occurrence from the group consisting of hydrogen, C_{1-4}alkyl C_{3-6}cycloalkyl, heterocyclyl and heterocyclylcarbonyl; wherein C_{1-4}alkyl and C_{3-6}cycloalkyl may be optionally substituted by one or more substituents selected from fluorine, hydroxyl, cyano, R^aR^bN—, R^aR^bN-carbonyl- and C_{1-3}alkoxy and wherein heterocyclyl and heterocyclylcarbonyl may be optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, halo-C_{1-6}-alkyl, hydroxyl-C_{1-6}-alkyl, R^aR^bN—C_{1-6}alkyl- and C_{1-6}-alkoxy-C_{1-6}-alkyl group; and wherein if said heterocyclyl or heterocyclylcarbonyl contains a —NH moiety that nitrogen may optionally be substituted by one or more groups C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$— and C_{1-6}-alkylcarbonyl;

or R^i and R^j taken together with the nitrogen to which they are attached may form a 4-7 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-7 membered heterocyclic ring may be optionally substituted on carbon by one or more substituents selected from the group consisting of fluorine, hydroxyl, oxo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, R^aR^bN—, R^aR^bN—SO_2— and R^aR^bN-carbonyl-; wherein said C_{1-6}alkyl or C_{1-6}alkoxy may optionally be substituted by fluorine, hydroxyl or cyano; and wherein the 4-7 membered heterocyclic ring may be optionally substituted on nitrogen by one or more substituents selected from the group consisting of C_{1-6}alkyl and R^aR^bN-carbonyl-; and wherein said C_{1-6}alkyl may be optionally substituted by one or more substituents selected from the group consisting of fluorine, hydroxyl, cyano;

R^P may be independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, cyano, C_{1-6}alkoxy, R^iR^jN—, R^iR^jN-carbonyl-, R^iR^jN—SO_2— and R^iR^jN-carbonyl-$N(R^a)$—;

and pharmaceutically acceptable salts, stereoisomers, esters and prodrugs thereof.

In certain embodiments, R^{A1} of the tricyclic compound of Formula IV may be hydrogen or fluorine.

In another embodiment, R^{A2} of the tricyclic compound of Formula IV may be selected from the group consisting of hydrogen, R^iR^jN, heterocyclyl, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, heterocyclyl-NR^a-carbonyl-C_{1-6}alkyl and heterocyclyl-carbonyl-NR^a—C_{1-6}alkyl; wherein said heterocyclyl may optionally be substituted by one or more groups R^g; and wherein if said heterocyclyl contains a —NH moiety, that nitrogen may optionally be substituted by on or more groups R^h; and wherein said C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}cycloalkyl and C_{1-6}alkoxy may optionally be substituted by one or more groups R^P.

Also provided herein are compounds that may be selected from the group consisting of: cis-(3aRS,9bRS)-7-(benzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid; cis-(3aRS,9bRS)-7-[2-(3-diethylaminopropyl)-4-fluorobenzenesulfonyl-amino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid; cis-(3aRS,9bRS)-7-[2-(3-{pyrrolidin-1-yl}propyl)-4-fluorobenzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid; cis-(3aRS,9bRS)-7-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid; cis-(3aR,9bR)-7-[2-

((Z)-3-diethylaminoprop-1-enyl)-4-fluoro-benzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid; cis-(3aS,9bS)-7-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid; 7-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,2-dihydrofuro[2,3-c]quinoline-6-carboxylic acid formate salt; 7-(benzenesulfonylamino))-1,2-dihydrofuro[2,3-c]quinoline-6-carboxylic acid formate salt; cis-(3aRS,9bRS)-7-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-6-carboxylic acid; (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-((E)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; cis-(3aRS,9bRS)-7-[2-(4-dimethylamino-butylamino)-benzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid; (1aR,7bS)-5-[2-(3-diethylaminopropyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2((Z)-3-ethylaminoprop-1-enyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2((Z)-3-ethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2((Z)-3-ethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-(pyrrolidin-1-yl)prop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-{2[(Z)-3-(pyrrolidin-1-yl)prop-1-enyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-{2[(Z)-3-(pyrrolidin-1-yl)prop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(3-dimethylaminopropylamino)-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-(3-dimethylaminopropylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2-(3-dimethylaminopropyl-amino)benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(4-dimethylaminobutylamino) benzenesulfonylamino]- 1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-(4-dimethylamino-butylamino)benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2-(4-dimethylaminobutylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(5-dimethylamino-pentylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-(propan-2-yl)aminoprop-1-enyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-((S)-3-hydroxypyrrolidin-1-yl) aminoprop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-((R)-3-hydroxypyrrolidin-1-yl) aminoprop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2((Z)-4-diethylaminobut-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2((Z)-4-diethylaminobut-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2-((Z)-4-diethylaminobut-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-(4-ethylpiperazin-1-yl)-ethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-(azetidin-1-yl)prop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-(3-hydroxy-azetidin-1-yl)prop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-(azetidin-1-yl)propyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2((Z)-4-diethylaminobutyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[N-(4-dimethylaminobutyl)-N-methylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-3-ylcarbamoyl)-methyl]-4-fluoro-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(1-ethylazetidin-3-yl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((R)-1-ethylpyrrolidin-3-ylcarbamoyl)methyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-(pyrrolidin-1-yl)-ethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-((R)-1-ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2-((R)-1-ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-((R)-1-ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-2-yl)cabonyl-aminomethyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(4-dimethylaminobutyrylamino)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid;

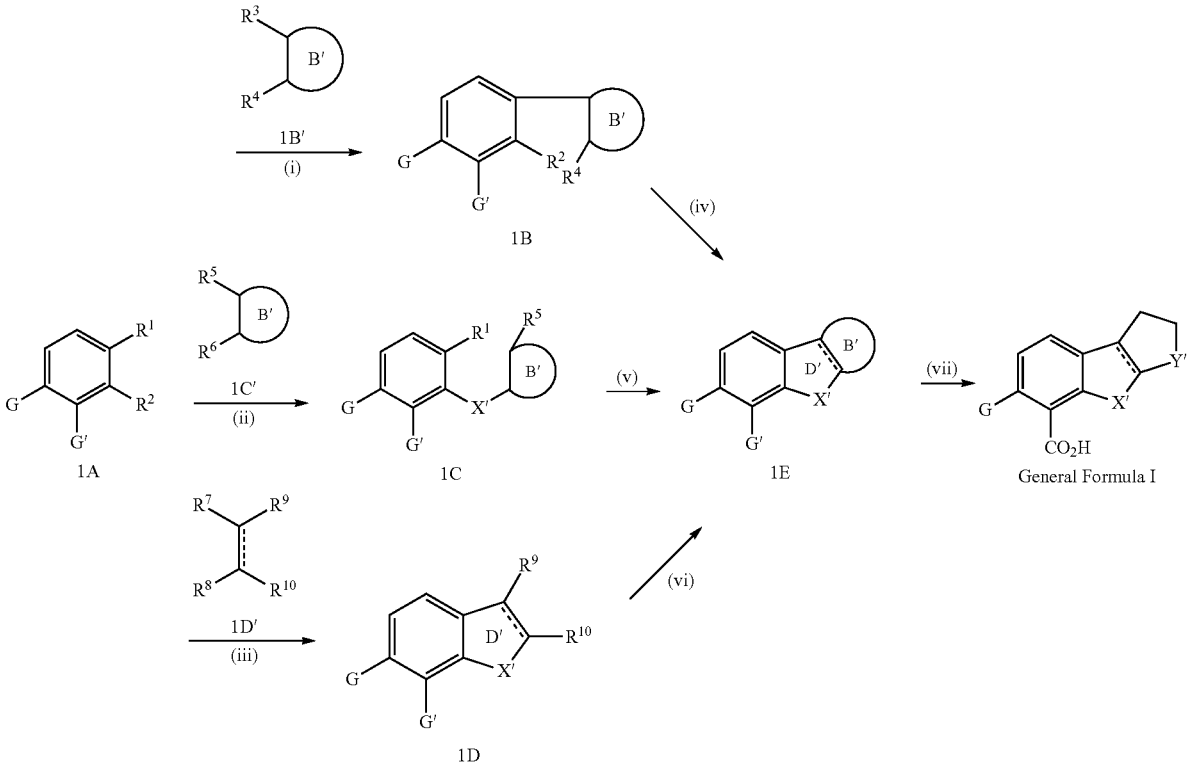
(1aRS,7bSR)-5-[2-((S)-1-ethyl-pyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(3-dimethylaminopropylcarbamoyl)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{[N—((S)-1-ethyl-pyrrolidin-3-yl)-N-methylcarbamoyl]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{[N—((R)-1-ethyl-pyrrolidin-3-yl)-N-methylcarbamoyl]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-((S)-1-ethylpyrrolidin-2-yl)ethylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-((R)-1-ethylpyrrolidin-2-yl)ethylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(3-N,N,-diethylaminopropylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{[((R)-1-ethylpyrrolidine-2-yl)carbonyl-amino]methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[(1-ethylazetidin-3-ylmethyl)amino]benzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-((Z)-3-diethylaminoprop-1-enyl)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{N—[((R)-1-ethylpyrrolidine-2-yl)carbonyl]-N-methyl-aminomethyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{N—[((S)-1-ethylpyrrolidine-2-yl)carbonyl]-N-methylamino-methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(4-dimethylaminobutylamino)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((R)-1-ethylpyrrolidin-3-ylmethyl)amino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-3-ylmethyl)amino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(4-ethyl-2-oxopiperazin-1-ylmethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(1-ethylpiperidin-4-ylmethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-(1-ethylazetidin-3-yl)ethyl]-4-fluoro-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((S)-1-azabicyclo[2.2.2]oct-3-yl)amino]benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((R)-1-azabicyclo-[2.2.2]oct-3-yl)amino]benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{[((S)-1-ethylpyrrolidine-3-carbonyl)amino]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-((R)-1-ethylpyrrolidin-3-ylamino)ethyl]-4-fluoro-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((R)-1-ethylpyrrolidin-3-yl)amino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-3-yl)amino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{[((R)-1-ethylpyrrolidine-3-carbonyl)amino]-methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-((Z)-3-diethylamino-2-methylprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-((R)-1-ethylpyrrolidin-3-yl)ethylamino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-((S)-1-ethylpyrrolidin-3-yl)ethylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-((S)-1-ethylpyrrolidin-3-yloxymethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-((R)-1-ethylpyrrolidin-3-yloxymethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-(1-ethylpiperidin-3-ylmethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-{2-[2-((R)-1-ethylpyrrolidin-2-yl)ethyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; and pharmaceutically acceptable salts, stereoisomers, esters and prodrugs thereof.

Procedures for making compounds described herein are provided below with reference to Schemes 1-3. In the reactions described below, it may be necessary to protect reactive functional groups (such as hydroxyl, amino, thio or carboxyl groups) to avoid their unwanted participation in the reactions. The incorporation of such groups, and the methods required to introduce and remove them are known to those skilled in the art (for example, see Greene, Wuts, Protective Groups in Organic Synthesis. 2nd Ed. (1999)). The deprotection step may be the final step in the synthesis such that the removal of protecting groups affords compounds of Formula I, as disclosed herein, or as exemplified in, for example, General Formula I, below. Starting materials used in the following schemes can be purchased or prepared by methods described in the chemical literature, or by adaptations thereof, using methods known by those skilled in the art. The order in which the steps are performed can vary depending on the groups introduced and the reagents used, but would be apparent to those skilled in the art.

The general synthetic strategy used to prepare the tricyclic compounds of General Formula I is depicted in Scheme 1. The tricyclic system may be assembled in a variety of ways, starting from an appropriately substituted and protected phenyl ring 1A. The group G' is a suitably protected carboxylic acid, such as a methyl- or t-butyl carboxylate or is a functional group that may be readily converted into a carboxylic acid, such as a nitrile or aldehyde. The group G is a sulfonamide group, or a functional group that may be subsequently converted into a sulfonamide group such as a suitably protected aniline. The B'-ring can be directly attached to the substituted phenyl ring to give intermediate 1B, and then the D'-ring can be formed by an intra-molecular reaction to give intermediate 1E. Alternatively, the B'-ring can be attached to the substituted phenyl ring 1A via a linker, X', to give intermediate 1C, and then the D'-ring can be formed by an intra-molecular reaction to give intermediate 1E. Alternatively, the D'-ring can be built up onto the substituted phenyl ring to give intermediate 1D, and then the B'-ring assembled to give intermediate 1E. Modifications to the B' and D' rings may be neces-

sary to provide the required saturated or partially unsaturated ring systems and this may be carried out prior to the formation of the tricyclic core or after it. For example, if the B' ring is a dihydro- or tetrahydrofuran it may be prepared from a corresponding furan compound by hydrogenation in the presence of a metal catalyst (for example palladium or palladium hydroxide on a solid support such as carbon) in a solvent (such as ethyl acetate, ethanol or dioxane) optionally in the presence of an acid (such as acetic acid). The hydrogenation may be carried out at any stage during the synthesis of the compounds either before or after the formation of the tricyclic core. Compounds of Formula I can be prepared from intermediate 1E by removal of any protecting groups. Alternatively, further modifications may be made to 1E, such as modifications at G, before the removal of any protecting groups to give compounds of General Formula I. Specific steps in the synthetic process are described in more detail below.

SCHEME 1



In Scheme 1, Step (i), compounds of structure 1A may be coupled under a range of conditions to compounds of structure 1B', where B' is an appropriate ring to afford compounds of the type 1B. The introduction of the B' ring may require a number of steps and the preparation of a number of intermediates. Protecting groups may also be required. If R^1 is a suitable group (such as a halide or triflate), 1B' can be converted to 1B by formation of a carbon-carbon bond. The carbon-carbon bond can be formed by reacting compounds of structure 1B' where R^3 is a borane, boronate or boronic acid group (such as a 2-formylfuran-3-boronate) in the presence of a palladium catalyst (such as palladium chloride dppf or tris-(dibenzylideneacetone)-dipalladium), in the presence of a base (such as cesium carbonate) and a suitable reagent (such as a phosphine, for example, tri-tert-butyl-phosphonium tetrafluoroborate or triphenylphosphine) in an appropriate solvent (such as dioxane, water or tetrahydrofuran, or mixtures thereof) and under appropriate conditions (such as heating, for example heating at 80-120° C. for 1-2 hours or microwave irradiation at 120-160° C. for 10 minutes to 1 hour) to afford 1B. A wide range of appropriate reagents and conditions are known to those skilled in the art to couple organoboranes, boronates and boronic acids to compounds such as 1A. [For example, see Miyaura, Suzuki, Chem. Rev. 1995, 95, 2457; Suzuki, Modern Arene Chemistry 2002, 53-106].

Alternatively the carbon-carbon bond in Scheme 1, Step (i) can be formed by coupling compounds of structure 1B' in which B' is an appropriate ring and where R^3 is a trialkylstannane (such as a tri-n-butylstannane) with compounds of structure 1A where R^1 is a suitable group (such as a halide of triflate) in the presence of a palladium catalyst (such as palladium chloride dppf), in an appropriate solvent (such as dimethoxyethane or tetrahydrofuran) and under appropriate conditions (such as heating, at 80-120° C. for 1-2 hours or by microwave irradiation at 120-160° C. for 10 minutes to 1 hour) to afford 1B. A wide range of appropriate reagents and conditions are known to those skilled in the art to couple stannanes to aryl halides such as 1A. [For example, see Smith, March, March's Advanced Organic Chemistry, 5th Edition, Wiley: New York, 2001, pp. 931-932; De Souza, Current Organic Synthesis 2006, 3(3), 313-326].

Alternatively compounds of structure 1A, where R^1 is a suitable group (such as a halide or triflate), can be treated with, for example, a diboronate (such as bis-pinacolatodiboron) in the presence of a palladium catalyst (such as palladium chloride dppf) and a base (such as potassium acetate or diiso-

propylamine) in an appropriate solvent (such as a mixture of dioxane and water) and under appropriate conditions (such as heating, for example at 80-120° C. for 1-2 hours or by microwave irradiation at 120-160° C. for 10 minutes to 1 hour) to give a compound of structure 1A, where R^1 is a boronate. A wide range of appropriate reagents and conditions are known to those skilled in the art to convert an aryl halide (or aryl triflate) to an arylboronate (or an arylborane) [for example, see Marshall Chemtracts 2000, 13(4), 219-222]. The arylboronate (or arylborane) thus formed, can then be treated with compounds of structure 1B' (where R^3 is a halogen or triflate) in the presence of suitable reagents such as a phosphine (for example tri-tert-butyl-phosphonium tetrafluoroborate), a base (such as cesium carbonate) and a catalyst (such as tris-(dibenzylideneacetone)-dipalladium) in an appropriate solvent (such as a mixture of water and dioxane) under appropriate conditions (such as heating at 80-120° C. for 1-2 hours or by microwave irradiation at 120-160° C. for 10 minutes to 1 hour) to afford compounds of structure 1B.

In Scheme 1, Step (iv), the groups R^2 and R^4 of compound 1B can be coupled together to give the group X', which forms the D'-ring. R^2 or R^4 may have been masked by protecting groups during Step (i), and may require deprotection before the group X' can be formed. Alternatively, R^2 or R^4 may require chemical modification before the group X' can be formed. For example if R^2 or R^4 is a nitro group, that group may be reduced, for example using hydrogen in the presence of a suitable catalyst (such as palladium on a solid support, such as carbon); or by treatment with an inorganic reducing agent (such as tin (II) chloride in DMF) to give an amino group. For example, if R^2 or R^4 is a hydroxyalkyl group, that group may be treated with an oxidising agent (such as Jones reagent or manganese dioxide) to give an aldehyde; or with a different oxidising agent (such as potassium permanganate) to give a carboxylic acid. For example, if R^2 or R^4 is an aldehyde, that group may be treated with an oxidising agent (such as potassium permanganate) to give a carboxylic acid or with a reducing agent (such as sodium borohydride) to give an alcohol. For example, if R^2 or R^4 is a ketone, that group may be treated with a reducing agent (such as sodium borohydride) to give a secondary alcohol. For example, if R^2 or R^4 is a carboxylic acid or ester, that group may be treated with a reducing agent (such as lithium aluminium hydride) to give an alcohol. For example, if R^2 or R^4 is an alkene group, that group may be treated with a borane (such as 9-borobicyclononane) and converted to a primary or secondary alcohol.

Formation of the linker X' may be carried out in a number of ways known to those skilled in the art. For example, if one of the two groups R^2 and R^4 is a hydroxyl and the other is a substituted alkylalcohol then 1B can be treated with a dehydrating agent (such as diisopropyl azodicarboxylate) in the presence of a phosphine, (such as triphenylphosphine) to give 1E, where X' is an ether. Alternatively, if one of the two groups R^2 or R^4 is a hydroxyl and the other group is an alkyl group substituted with a leaving group (such as a halogen, tosylate or triflate) 1B can be treated with a base (such as diisopropylethylamine, potassium carbonate or sodium hydride) to form 1E, where X' is an ether.

Alternatively, if one of the groups R^2 or R^4 is a carboxylic acid and the other group is an alkyl halide or sulfonate, then 1B can be treated with a base such as diisopropylethylamine, potassium carbonate or sodium hydride to form 1E, where X' is an ester.

Alternatively, if one of the two groups R^2 or R^4 is a hydroxyl, or substituted alkylalcohol and the other group is a carboxylic acid or carboxylic ester, then 1B can be treated with an acid (such as hydrochloric acid) or dehydrating agent (such as dicyclohexylcarbodiimide or acetic anhydride) to form 1E, where X' is an ester.

Alternatively, if one of the two groups R^2 or R^4 on 1B is a hydroxyl or substituted alkylalcohol and the other group is a carboxylic acid, then the carboxylic acid can first be converted to a mixed anhydride (for example by treatment with 2,4,6-trichlorobenzoyl chloride) or to an activated ester (for example by treatment with HATU in the presence of a base such as diisopropylethylamine or pyridine), and the resulting mixed anhydride or activated ester can be further treated with a base (such as diisopropylethylamine, pyridine or potassium carbonate) to form 1E, where X' is an ester.

Alternatively, if one of the groups R^2 or R^4 on 1B is an amine or a substituted alkylamine and the other group is a carboxylic acid, the carboxylic acid can be converted to an activated ester (for example by treatment with HATU and a base such as diisopropylethylamine or pyridine or TBTU in the presence of N-methylmorpholine), and the resulting activated ester can be further treated with a base to form 1E where X' is an amide.

Alternatively, if one of the two groups R^2 or R^4 on 1B is an amine, or a substituted alkylamine and the other group is a carboxylic acid, then 1B can then be treated with a dehydrating agent (such as such as diisopropylcarbodiimide) to form 1E, where X' is an amide.

Alternatively, if one of the two groups R^2 or R^4 is an amine, or substituted alkylamine and the other group is an alkyl group substituted with a leaving group (such as a halogen, tosylate or triflate) then 1B can be treated with a base (such as diisopropylethylamine, pyridine or potassium carbonate) to form 1E, where X' is a substituted amine.

Alternatively, if one of the two groups R^2 or R^4 is an aldehyde, and the other group is a phosphorane (such as an alkyl triphenylphosphorane) or an alkyl phosphonate (such as an alkyl phosphonic acid diethyl ester) then 1B can be treated with a base (such as diisopropylethylamine, potassium carbonate or sodium hexamethyldisilazide) to form 1E, where X' is an alkene which may, or may not be further substituted.

Alternatively, if one of the two groups R^2 or R^4 is an amine and the other group is an aldehyde then 1B can be treated with an acid (such as p-toluenesulfoniic acid) or a Lewis acid (such as tin tetrachloride) to give 1E, where X' is —CR═N— or —N═CR—.

In Scheme 1, Step (ii), compounds of the structure 1A can be reacted with 1C' to form the linker X' and give compounds of the structure 1C. The formation of the linker X' in compounds with the structure 1C may require a number of steps and the preparation of a number of intermediates, and the use of protecting groups may also be required.

For example, if one of the two groups R^2 or R^6 is a hydroxyl group and the other group is a substituted alkylalcohol then 1A and 1C' can be treated with a dehydrating agent (such as diisopropyl azodicarboxylate) in the presence of a phosphine, (such as triphenylphosphine) to give 1C, where X' is an ether. Alternatively, if one of the two groups R^2 or R^4 is a hydroxyl and the other group is an alkyl group substituted with a leaving group (such as a halogen, or a mesylate) 1A and 1C' can be treated with a base (such as diisopropylethylamine, potassium carbonate or sodium hydride) to form 1C, where X' is an ether.

Alternatively, in Scheme 1, Step (ii), if one of the two groups R^2 or R^6 is a hydroxyl, or alkylalcohol and the other group is a carboxylic acid, then the carboxylic acid can be converted to an acyl halide (for example by treatment with thionyl chloride or oxalyl chloride), or to a mixed anhydride (for example by treatment with 2,4,6-trichlorobenzoyl chlo-

ride in the presence of a base such as diisopropylethylamine) or to an activated ester (for example by treatment with HATU in the presence of a base such as diisopropylethylamine or pyridine, or treatment with diisopropylcarbodiimide in the presence of HOBT), then 1A and 1C' can be combined to form 1C, where X' is an ester.

Alternatively, if one of the two groups R^2 or R^6 is an amine, or alkylamine and the other group is a carboxylic acid, then the carboxylic acid can be converted to an acyl halide (for example by treatment with thionyl chloride or oxalyl chloride), or to a mixed anhydride (for example by treatment with 2,4,6-trichlorobenzoyl chloride in the presence of a base such as diisopropylethylamine), or to an activated ester (for example by treatment with HATU in the presence of disopropylethylamine or pyridine, or treatment with diisopropylcarbodiimide in the presence of HOBT), then 1A and 1C' can be combined to form 1C, where X' is an amide.

Alternatively, if one of the two groups R^2 or R^6 is an amine, or substituted alkylamine and the other group is an alkyl group substituted with a leaving group (such as a halogen, or a triflate) then 1A and 1C' can be treated with a base (such as diisopropylethylamine, pyridine or potassium carbonate) to form 1C, where X' is a substituted amine.

Alternatively, if one of the two groups R^2 or R^6 is an aldehyde, and the other group is a phosphorane (such as an alkyltriphenylphosphorane) or an alkylphosphonate (such as an alkylphosphonic acid diethyl ester) then 1A and 1C' can be treated with a base (such as diisopropylethylamine or potassium carbonate or sodium hexamethyldisilazide) to form 1C, where X' is an alkene which may, or may not be further substituted.

In Scheme 1, Step (v), compounds of structure 1E may be prepared from compounds of structure 1C by reaction of the groups R^1 and R^5 under a range of conditions to form a carbon-carbon bond. If one of the groups R^1 or R^5 is a suitable group (such as a halide or triflate), and the other group is a borane, boronate or boronic acid then, in the presence of a palladium catalyst (such as palladium chloride dppf), and in the presence of a base (such as cesium carbonate), in an appropriate solvent (such as dioxane, water or tetrahydrofuran or mixtures thereof) and under appropriate conditions (such as heating, for example heating at 80-120° C. for 1-2 hours or microwave irradiation at 120-160° C. for 10 minutes to 1 hour), 1C can be converted into 1E. A wide range of appropriate reagents and conditions are known to those skilled in the art to couple organoboranes, boronates and boronic acids to give compounds of the type 1E.

Alternatively, if one of the groups R^1 or R^5 is a suitable group (such as a halide or triflate), and the other group is a trialkylstannane, the carbon-carbon bond can be formed in the presence of a palladium catalyst (such as palladium chloride dppf), in an appropriate solvent (such as dimethoxyethane or tetrahydrofuran) and under appropriate conditions (such as heating, at 80-120° C. for 1-2 hours or by microwave irradiation at 120-160° C. for 10 minutes to 1 hour) to afford 1E. A wide range of appropriate reagents and conditions are known to those skilled in the art to couple aryl or heteroaryl stannanes to aryl or heteroaryl halides.

In Scheme 1, Step (iii), compounds of structure 1A may be reacted under a range of conditions with intermediates of the type 1D' to give compounds of structure 1D where D' is a six- or seven-membered fused heterocyclic ring and R^9 and R^{10} are suitable functional groups that may be used to form the B'-ring. The groups R^1 and R^7 may be reacted together to form a carbon-carbon bond, and the groups R^2 and R^8 may be reacted together to form the group X'. Methods to form bicyclic compounds of structure 1D from substituted phenyl rings of structure 1A are well known to those skilled in the art (see Comprehensive Heterocyclic Chemistry Ed.: Katritzky, Ramsden, Scriven, and Taylor, Elsevier, 2008).

For example, a compound of structure 1A, where R^2 is a hydroxyl group and R^1 is hydrogen, can be treated with a suitably protected and substituted 3-halo-propanoic acid or ester in an appropriate solvent (such as tetrahydrofuran or dimethylformamide) and in the presence of a base (such as sodium carbonate or diisopropylethylamine) at a temperature between room temperature and the reflux temperature of the solvent to give a compound of the type 1A, where R^2 is a substituted oxypropanoic acid or ester. This intermediate may be treated with a suitable reagent (such as a strong acid, for example triflic acid) to give 1D where R^9 is oxo, R^{10} is hydrogen and X' is —OCH_2—.

Alternatively, a compound of structure 1A, where R^2 is a hydroxyl and R^1 is hydrogen, can be treated with a propargyl halide or tosylate in the presence of a base (such as potassium carbonate or cesium carbonate) in a solvent (such as acetone) at a temperature between room temperature and the reflux temperature of the solvent to give a compound of type 1A in which R^2 is a propargyloxyl group. This intermediate may be heated to ~200° C. or treated with an appropriate catalyst (such as a gold catalyst, for example triphenylphosphine gold triflamide) in an appropriate solvent (such as toluene) at a temperature between 80° C. and the reflux temperature of the solvent to give a compound of structure 1D wherein X' is —OCH_2—, R^9 and R^{10} are H and the bond between is a double bond (i.e. a chromene).

Further modification of the intermediates of structure 1D having a double bond between the carbons that R^9 and R^{10} are attached to (such as a chromene) may be achieved, for example, by treatment with a hydroborating agent (such as borane-THF complex) followed by oxidation with, for example, hydrogen peroxide to give a mixture of compounds of structure 1D wherein X' is OCH_2, R^9 is H and R^{10} is a hydroxyl group and wherein X' is —OCH_2—, R^9 is a hydroxyl and R^{10} is H which may be separated by chromatography.

Further modification of an intermediate of structure 1D in which one of R^9 and R^{10} is H and the other is a hydroxyl may be carried out. For example, the intermediate may be oxidized by treatment with an oxidizing agent (such as Dess Martin periodinane) to give a compound of structure 1D in which one of R^9 and R^{10} is H the other is oxo.

Alternatively, a compound of structure 1A in which R^1 is an appropriate group (such as a halogen, for example bromine or iodine, or a triflate) and R^2 is a protected amine (such as an acetamide or a trifluoroacetamide) may be coupled with a terminal alkyne in the presence of a palladium catalyst (such as tetrakis(triphenylphosphine) palladium (0)) optionally in the presence of an additional copper catalyst (such as copper (I) iodide) in the presence of a base or salt (such as triethylamine or potassium acetate), in a solvent (such as tetrahydrofuran or dimethylformamide) at a temperature between room temperature and the reflux temperature of the solvent or by irradiation in the microwave at a temperature between 100° C. and 160° C. to give a compound of structure 1A in which R^1 is a substituted alkyne and R^2 is a protected amine (such as an acetamide or a trifluoroacetamide). Alternatively, a compound of structure 1A in which R^1 is an appropriate group (such as a halogen, for example bromine or iodine, or a triflate) and R^2 is a protected amine (such as an acetamide or a trifluoroacetamide) may be coupled with an acetylenic stannane in the presence of a palladium catalyst (such as palladium chloride dppf) in an appropriate solvent (such as dioxane, dimethoxyethane or tetrahydrofuran) at a temperature between room temperature and the reflux temperature of the

solvent or alternatively by irradiation in the microwave at a temperature between 100° C. and 160° C. to give a compound of structure 1A in which R^1 is an alkyne and R^2 is a protected amine (such as an acetamide or a trifluoroacetamide).

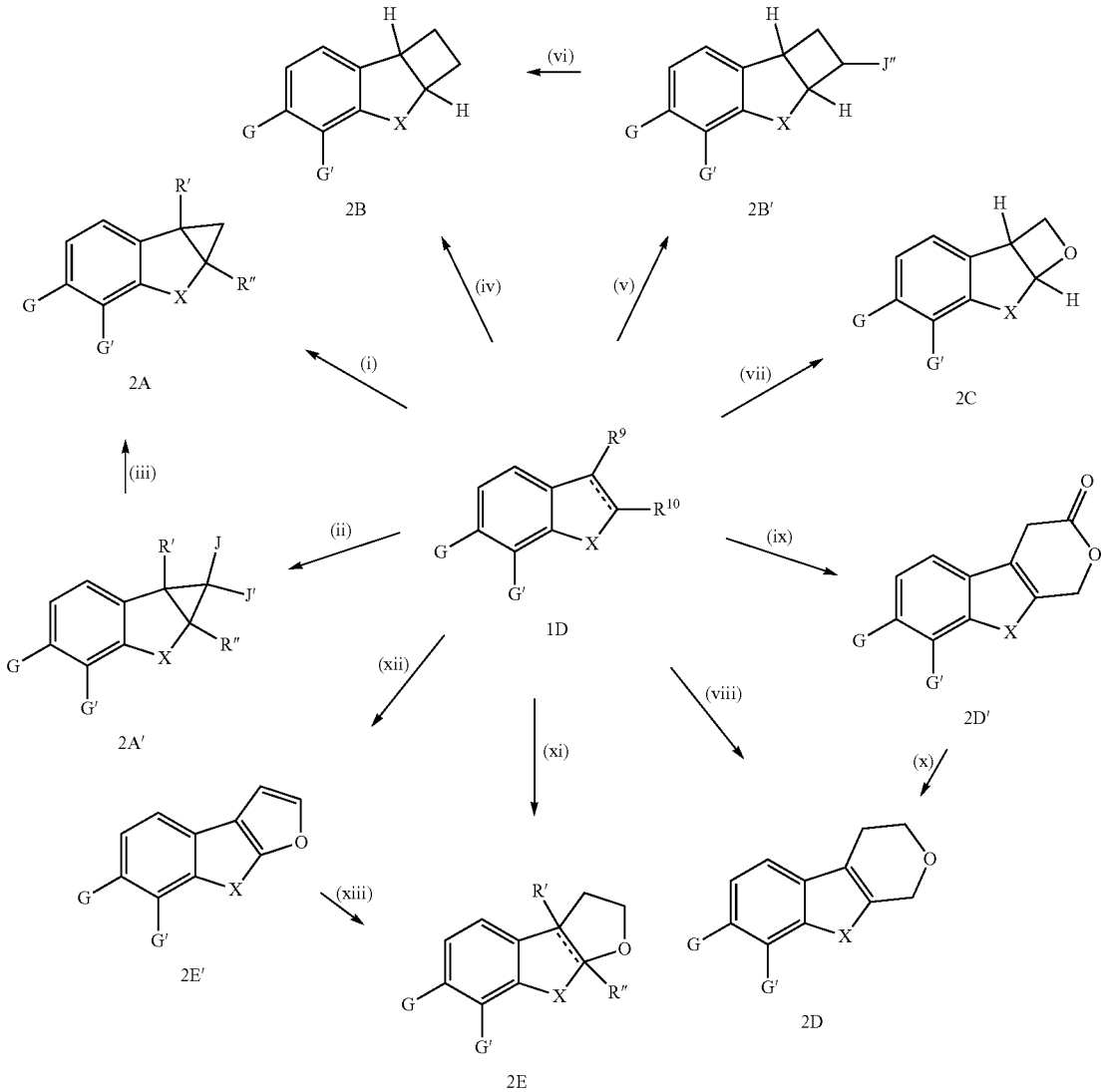
In Scheme 1, Step (iii), a compound of structure 1A in which R^1 is an appropriately substituted alkyne and R^2 is a protected amine (such as an acetamide of a trifluoroacetamide) may be treated with a base (such as potassium carbonate or sodium methoxide) in an appropriate solvent (such as acetone, DMF or methanol) at a temperature between room temperature and the reflux temperature of the solvent to give a compound of structure 1D in which X' is NH. Alternatively, a compound of structure 1A in which R^1 is an appropriately substituted alkyne and R^2 is a protected amine (such as an acetamide of a trifluoroacetamide) may be treated with a palladium catalyst (such as bis-(triphenylphosphine)palladium chloride) in the presence of a base (such as triethylamine) and an appropriate catalyst (such as copper(I) iodide) in a solvent (such as dimethylformamide) at a temperature between room temperature and the reflux temperature of the solvent to give a compound of structure 1D in which X' is NH.

The general synthetic strategy to elaborate 1D is shown in Scheme 2.

In Scheme 2, compounds of structure 1D may be converted to a variety of compounds of structure 1E using reactions known to those skilled and the art. In some cases modifications to the groups R^9 and R^{10}, in 1D may be required with diazomethane in order to be able to generate the require ring systems. One skilled in the art will recognize that it may be necessary for various functional groups to be protected prior to reaction. Specific steps in the synthetic procedures are described in more detail below.

In Scheme 2, Step (i), 1D in which R^9 and R^{10} are both H and the bond between the carbon atoms is a double bond, may be treated with diethyl zinc and di-iodomethane optionally in the presence of additional reagents (such as trifluoroacetic acid or zinc iodide) in a solvent (such as 1,2-dichloroethane) at a temperature between −78° C. and room temperature to give compounds of structure 2A in which the B' ring is a cyclopropyl ring. Alternatively, compounds of structure 1D in which R^9 and R^{10} are both H and the bond between the carbon atoms is a double bond, may be treated with trimethyl sulfoxonium iodide or trimethyl sulphonium iodide in the presence of a base (such as sodium hydride) in a solvent (such as

SCHEME 2



dimethyl sulfoxide) at a temperature between room temperature and 100° C. Alternatively, compounds of structure 1D in which R^9 and R^{10} are both H and the bond between the carbon atoms is a double bond, may be treated with diazomethane in the presence of a catalyst (such as palladium acetate) in a solvent such as diethyl ether at a temperature between 0° C. and room temperature.

Alternatively, compounds of structure 2A may be prepared in a two step procedure. For example, in Scheme 2, Step (ii), 1D in which R^9 and R^{10} are both H and the bond between the carbon atoms is a double bond, may be treated with trimethylsilyl diazomethane in the presence of a catalyst (such as palladium acetate) in a solvent (such as diethyl ether) at a temperature between 0° C. and room temperature to give the intermediate 2A' in which J is H and J' is a trimethyl silyl group. In Scheme 2, Step (iii), intermediates 2A' in which J is H and J' is a trimethyl silyl group may be converted to compounds of structure 2A by treatment with a source of fluoride, (for example tetrabutyl ammonium fluoride) in a solvent (such as tetrahydrofuran) at a temperature between 0° C. and room temperature.

Alternatively in Scheme 2, Step (ii), 1D in which R^9 and R^{10} are both H and the bond between the carbon atoms is a double bond, may be treated with a haloform (such as chloroform or bromoform) in the presence of a base such as sodium hydroxide or potassium t-butoxide in the presence of a catalyst (such as triethylbenzylammonium chloride or tetrabutyl ammonium bromide) in a mixture of water and a halogenated solvent (such as dichloromethane or dichloroethane) or alternatively in excess of the haloform at a temperature between room temperature and 80° C. to give the intermediate 2A' in which J and J' are both chlorine or bromine. In Scheme 2, Step (iii), the intermediates 2A' in which J and J' are both chlorine or bromine may be converted to compounds of structure 2A by treatment with a base (such as sodium methoxide or sodium t-butoxide) in a solvent (such as tetrahydrofuran) at a temperature between room temperature and the reflux temperature of the solvent. Alternatively, the intermediates 2A' in which J and J' are both chlorine or bromine may be converted to compounds of structure 2A by reduction; for example, by treatment with lithium aluminium hydride in a solvent (such as tetrahydrofuran) at a temperature between 0° C. and the reflux temperature of the solvent or alternatively, for example by hydrogenation using a catalyst (such as palladium on carbon) in a solvent (such as methanol or ethanol), optionally in the presence of a base (such as triethylamine). Alternatively, the intermediates 2A' in which J and J' are both chlorine or bromine may be converted to compounds of structure 2A under radical conditions; for example, by treatment with a tin hydride (such as tributyl tin hydride) optionally in the presence of a radical initiator (such as azo-bis-isobutyronitrile) in a solvent (such as toluene) at a temperature between room temperature and the reflux temperature of the solvent.

In Scheme 2, Step (iv), 1D in which X' includes a carbonyl (for example where X' is —O—C(O)—) and R^9 and R^{10} are both H and the bond between the carbon atoms is a double bond, may be converted to the corresponding compounds 2B by treatment with ethylene in a solvent (such as dichloromethane) under photochemical conditions.

Alternatively compounds of structure 2B may be prepared in a multi-step procedure. For example, in Scheme 2, Step (v), 1D in which both R^9 and R^{10} are both H and the bond between the two carbon atoms is a double bond may be treated with an acrylate (such as ethyl acrylate) in a solvent (such as acetonitrile) under photochemical conditions to give an intermediate 2B' in which J'' is an ester group (such as an ethyl ester). The ester may be hydrolysed by, for example, treatment with sodium hydroxide or lithium hydroxide in a solvent such as aqueous ethanol or aqueous dioxane at a temperature between room temperature and the reflux temperature of the solvent to give an intermediate of structure 2B' in which J'' is a carboxylic acid. In Scheme 2, Step (vi), the acid may be removed for example by heating in, for example, quinoline optionally in the presence of a catalyst (such as copper) to around 200° C.

In Scheme 2, Step (vii), 1D in which R^{10} is a hydroxyl and R^9 is a group CH_2OH may be treated with a sulfonyl chloride (such as 4-toluenesulfonyl chloride or methanesulfonyl chloride) in the presence of a base (such as triethylamine), optionally in the presence of 4-dimethylaminopyridine, in a solvent (such as dichloromethane or toluene) at a temperature between room temperature and the reflux temperature of the solvent. The product may be treated with a base (such as triethylamine, diisopropylethylamine or sodium hydride) in an appropriate solvent (such as dichloromethane, tetrahydrofuran or DMF) to give a compound of structure 2C.

In Scheme 2, Step (viii), 1D in which R^9 is CH_2CH_2OH and R^{10} is CH_2OH may be converted to compounds 2D. One of the hydroxyl groups may need to be protected and the other is treated with a sulfonyl chloride (such as 4-toluenesulfonyl chloride or methanesulfonyl chloride) in the presence of a base (such as triethylamine) optionally in the presence of 4-dimethylaminopyridine, in a solvent (such as dichloromethane or toluene) at a temperature between room temperature and the reflux temperature of the solvent. After deprotection of the remaining hydroxyl group, the intermediate may be treated with a base (such as triethylamine, diisopropylethylamine or sodium hydride) in a solvent (such as dichloromethane, tetrahydrofuran or dimethylformamide at a temperature between room temperature and the reflux temperature of the solvent to give a compound of structure 2D.

Alternatively, compounds of structure 2D may be prepared in a 2 step procedure. For example, in Scheme 2, Step (ix), 1D in which R^9 is CH_2CO_2H and R^{10} is CH_2OH may be converted to compounds of structure 2D'. The carboxylic acid may be converted to an acid chloride (by treatment with, for example, thionyl chloride or oxalyl chloride, optionally in the presence of a catalytic amount of DMF in a solvent such as dichloromethane or toluene) or to a mixed anhydride (for example by treatment with 2,4,6-trichlorobenzoyl chloride in the presence of a base such as diisopropylethylamine) or to an activated ester (for example by treatment with HATU in the presence of a base such as diisopropylethylamine or pyridine, or treatment with diisopropylcarbodiimide in the presence of HOBT). The acid chloride, mixed anhydride or activated ester may then be treated with a base (such as triethylamine or pyridine), in a solvent (such dichloromethane or toluene) to give the compound of structure 2D'. In Scheme 2, Step (x), compounds of structure 2D' may be converted to compounds of structure 2D by reduction, for example, by treatment with lithium aluminium hydride, sodium diisobutylaluminium hydride or borane-dimethyl sulfide complex, in an appropriate solvent (such as tetrahydrofuran) at a temperature between −78° C. and room temperature.

In Scheme 2, Step (xi), 1D in which R^9 is CH_2CH_2OH and R^{10} is a hydroxyl may be treated with a sulfonyl chloride (such as 4-toluenesulfonyl chloride or methanesulfonyl chloride) in the presence of a base (such as triethylamine), optionally in the presence of 4-dimethylaminopyridine, in a solvent (such as dichloromethane or toluene) at a temperature between room temperature and the reflux temperature of the solvent, followed by treatment with a base (such as triethylamine, diisopropylethylamine or sodium hydride) in an appropriate solvent (such as dichloromethane, tetrahydrofu-

ran or DMF) at a temperature between room temperature and the reflux temperature of the solvent to give a compound of structure 2E.

Alternatively, compounds of structure 2E may be prepared in a 2 step procedure. In Scheme 2, Step (xii), 1D in which R^9 is H and R^{10} is oxo may be converted to compounds of structure 2E' by treatment with chloroacetaldehyde or bromoacetaldehyde in the presence of an aqueous base (such as sodium bicarbonate or sodium hydroxide in water) at a temperature between 0° C. and room temperature, followed by treatment with an acid (such as concentrated sulfuric acid) in a mixture of water and an organic solvent (such as ethyl acetate).

In Scheme 2, Step (xiii), compounds of structure 2E may be prepared from compounds of structure 2E' by hydrogenation in the presence of a metal catalyst (such as palladium or palladium hydroxide on a solid support such as carbon) in a solvent (such as an ether, for example tetrahydrofuran or dioxane, or an alcohol, such as methanol or ethanol), optionally in the presence of an acid (such as acetic acid). Depending upon the nature of the linker X', the bond between the two rings may be reduced or not to give either a tetrahydrofuran or a dihydrofuran. For example, if X' is —N═C— then the B' ring in 2E will be a dihydrofuran whereas if X' is —OCH_2— then the B' ring will be a tetrahydrofuran.

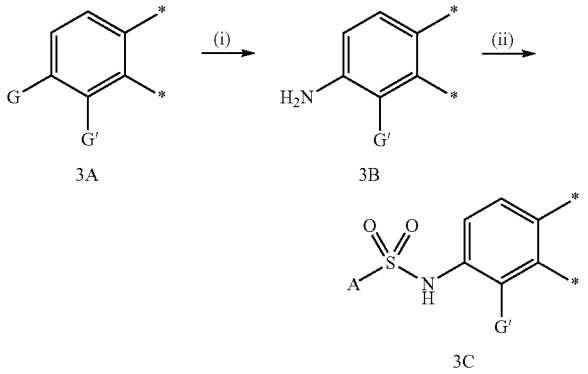
In Scheme 1, Step (vii), compounds of general structure 1E may be converted to compounds of General Formula I by the conversion of the group G' to a carboxylic acid. If the group G' is a carboxylic ester (such as a methyl, tert-butyl or benzyl ester) then a variety of reagents and conditions can be used to convert 1E into a compound of the General Formula I. For example, if G' is a methyl, ethyl or benzyl ester, it may be converted to a carboxylic acid by treatment with an inorganic base (such as lithium hydroxide or sodium hydroxide) in a solvent (such as methanol, dioxane or water, or mixtures thereof) at a temperature between room temperature and the reflux temperature of the solvent, or alternatively by microwave irradiation at 120-180° C. for 10 minutes to 1 hour. Alternatively if G' is a benzyl ester it may be converted to a carboxylic acid by hydrogenation in the presence of a catalyst (such as palladium on a solid support such as carbon) in a solvent (such as dioxane or ethyl acetate). Alternatively if G' is a tert-butyl ester, it may be converted to a carboxylic acid by treatment with an acid (such as trifluoromethanesulfonic acid or hydrogen chloride) in a solvent (such as dichloromethane or dioxane).

Alternatively, if the group G' is a nitrile, it may be converted into a carboxylic acid by treatment with aqueous acid (such as a mineral acid, for example hydrochloric acid) under appropriate conditions (such as heating, for example to reflux); or by treatment with aqueous base (such as an aqueous hydroxide, for example aqueous sodium hydroxide) under appropriate conditions (such as heating, for example to reflux).

Alternatively, if the group G' is an aldehyde (CHO) or a hydroxymethyl (CH_2OH) moiety then it may be converted into a carboxylic acid by treatment with a suitable oxidising reagent (such as potassium permanganate or chromic acid).

The general synthetic strategy to modify the group G is depicted in Scheme 3. The G group may be introduced and/or modified either before, during or after the assembly of the tricyclic ring system. Specific steps used to assemble sulfonamide are described in more detail below.

SCHEME 3



In Scheme 3, the asterisks denote either the presence of the groups R^1 and R^2 (as shown in Scheme 1) or the presence of the D' and B' rings, or intermediates towards the preparation of the rings (as shown in Schemes 1 and 2).

In Scheme 3, Step (i), compounds of structure 3A in which G is a nitro group may be converted to compounds 3B by reduction, for example by catalytic hydrogenation in the presence of a metal catalyst (such as palladium on a solid support such as carbon) in a solvent (such as an ether, for example tetrahydrofuran, or an alcohol, for example methanol or ethanol). Alternatively, compounds of structure 3A in which G is a nitro group may be converted to compounds of structure 3B by chemical reduction. For example, the reduction may be achieved using a metal or metal salt (such as iron, zinc or tin (II) chloride) in the presence of an acid (such as hydrochloric acid or acetic acid).

In Scheme 3, Step (i), compounds of structure 3A in which G is a protected amino group may be converted to compounds of structure 3B by removal of the protecting groups. Protecting groups for amino groups are well known to those skilled in the art and methods for their removal are equally well known [for example, see Greene, Wuts, Protective Groups in Organic Synthesis. 2nd Ed. (1999)]. For example, compounds of structure 3A in which F is an amino group protected with one or two Boc groups may be converted to compounds of structure 3B by treatment with an acid (such as trifluoroacetic acid, formic acid or hydrogen chloride) in a solvent (such as dichloromethane or dioxane).

Alternatively, in Scheme 3, Step (i), compounds of structure 3A in which G is a pivaloyl protected aniline may be converted to compounds of structure 3B by treatment with an acid (such as concentrated sulfuric acid) in a solvent (such as methanol) at a temperature between room temperature and the reflux temperature of the solvent.

In Scheme 3, Step (ii), compounds of structure 3B may be converted to compounds of structure 3C by treatment with an appropriate sulfonyl chloride (such as a substituted or unsubstituted benzene sulfonyl chloride) or an activated sulfonate ester (such as a pentafluorophenyl sulfonate ester) in the presence of a suitable base (such as pyridine, diisopropylethylamine or cesium carbonate) in a suitable solvent (such as dichloromethane or dimethylformamide) at a temperature between room temperature and the reflux temperature of the solvent.

Intermediates towards the preparation of compounds of Formula I or, for example, General Formula I may require reduction of an aromatic ring system to give the saturated ring system required in the compounds of Formula 1. This hydro-

genation may be carried out by hydrogenation of the intermediates in the presence of a metal catalyst (for example palladium or palladium hydroxide on a solid support, such as carbon) in a solvent (such as ethanol, ethyl acetate or dioxane) optionally in the presence of an acid (such as acetic acid). The reduction of the aromatic rings may be carried out before the formation of the tricyclic ring system or after it or at any stage during the synsthesis as will be recognized by those skilled in the art.

Compounds of any of Formula I, Formula II or, for example, General Formula I as depicted above, or any of the intermediates described in the schemes above, can be further derivatised by using one or more standard synthetic methods known to those skilled in the art. Such methods can involve substitution, oxidation or reduction reactions. These methods can also be used to obtain or modify compounds of General Formula I or any preceding intermediates by modifying, introducing or removing appropriate functional groups. Particular substitution approaches include alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulfonylation, nitration, formylation, hydrolysis and coupling procedures. These procedures can be used to introduce a functional group onto the parent molecule (such as the nitration or sulfonylation of aromatic rings) or to couple two molecules together (for example to couple an amine to a carboxylic acid to afford an amide; or to form a carbon-carbon bond between two heterocycles). For example, alcohol or phenol groups can be converted to ether groups by coupling a phenol with an alcohol in a solvent (such as tetrahydrofuran) in the presence of a phosphine (such as triphenylphosphine) and a dehydrating agent (such as diethyl, diisopropyl or dimethyl azodicarboxylate). Alternatively, ether groups can be prepared by deprotonation of an alcohol, using a suitable base (such as sodium hydride) followed by the addition of an alkylating agent (such as an alkyl halide or an alkyl sulfonate).

In another example, a primary or secondary amine can be alkylated using a reductive alkylation procedure. For example, the amine can be treated with an aldehyde and a borohydride (such as sodium triacetoxyborohydride, or sodium cyanoborohydride in a solvent (such as a halogenated hydrocarbon, for example dichloromethane, or an alcohol, for example ethanol) and, where necessary, in the presence of an acid (such as acetic acid).

In another example, hydroxy groups (including phenolic OH groups) can be converted into leaving groups, such as halogen atoms or sulfonyloxy groups (such as alkylsulfonyloxy, for example trifluoromethanesulfonyloxy, or aryl suphonyloxy, for example p-toluenesulfonyloxy) using conditions known to those skilled in the art. For example, an aliphatic alcohol can be reacted with thionyl chloride in a halogenated hydrocarbon (such as dichloromethane) to afford the corresponding alkyl chloride. A base (such as triethylamine) can also be used in the reaction.

In another example, ester groups can be converted to the corresponding carboxylic acid by acid- or base-catalysed hydrolysis depending on the nature of the ester group. Acid catalysed hydrolysis can be achieved by treatment with an organic or inorganic acid (such as trifluoroacetic acid in an aqueous solvent, or a mineral acid such as hydrochloric acid in a solvent such as dioxane). Base catalysed hydrolysis can be achieved by treatment with an alkali metal hydroxide (such as lithium hydroxide in an aqueous alcohol, for example methanol).

In another example, aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange by treatment with a base (such as a lithium base, for example n-butyl or t-butyl lithium) optionally at a low temperature (such as −78° C.) in a solvent (such as tetrahydrofuran) and the mixture may then be quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group can be introduced by using dimethylformamide as the electrophile. Aromatic halogen substituents can also be subjected to palladium catalysed reactions to introduce groups such as carboxylic acids, esters, cyano or amino substituents.

In another example, an aryl, or heteroaryl ring substituted with an appropriate leaving group (such as a halogen or sulfonyl ester, for example a triflate) can undergo a palladium catalysed coupling reaction with a wide variety of substrates to form a carbon-carbon bond. For example, a Heck reaction can be used to couple such a ring system to an alkene (which may, or may not, be further substituted) by treatment with an organopalladium complex (such as tetrakis(triphenylphosphine)palladium(0), palladium (II) acetate or palladium (II) chloride) in the presence of a ligand (such as a phosphine, for example triphenylphosphine) in the presence of a base (such as potassium carbonate or a tertiary amine, for example, triethylamine), in an appropriate solvent (such as tetrahydrofuran or DMF), under appropriate conditions (such as heating to, for example, 50-120° C.). In another example, a Sonogashira reaction can be used to couple such a ring system to an alkyne (which may, or may not be further substituted) by treatment with a palladium complex (such as tetrakis(triphenylphosphine)palladium(0)) and a halide salt of copper (I) (such as copper (I) iodide), in the presence of a base (such as a potassium carbonate or a tertiary amine, for example, triethylamine), in an appropriate solvent (such as tetrahydrofuran or dimethylformamide), under appropriate conditions (such as heating to, for example, 50-120° C.). In another example, a Stille reaction can be used to couple such a ring system to an alkene, by treatment with an organotin compound (such as an alkynyltin or alkenyltin reagent, for example an alkenyltributylstannane) in the presence of a palladium complex (such as tetrakis(triphenylphosphine)palladium(0)), with, or without the presence of a salt (such as a copper (I) halide), in an appropriate solvent (such as dioxane or dimethylformamide), under appropriate conditions (such as heating to, for example, 50-120° C.).

Particular oxidation approaches include dehydrogenations and aromatisation, decarboxylation and the addition of oxygen to certain functional groups. For example, aldehyde groups can be prepared by oxidation of the corresponding alcohol using conditions well known to those skilled in the art. For example, an alcohol can be treated with an oxidising agent (such as Dess-Martin periodinane) in a solvent (such as a halogenated hydrocarbon, for example dichloromethane). Alternative oxidising conditions can be used, such as treatment with oxalyl chloride and an activating amount of dimethylsulfoxide and subsequent quenching by the addition of an amine (such as triethylamine). Such a reaction can be carried out in an appropriate solvent (such as a halogenated hydrocarbon, for example dichloromethane) and under appropriate conditions (such as cooling below room temperature, for example to −78° C. followed by warming to room temperature). In another example, sulfur atoms can be oxidised to the corresponding sulfoxide or sulfone using an oxidising agent (such as a peroxy acid, for example 3-chloroperoxybenzoic acid) in an inert solvent (such as a halogenated hydrocarbon, for example dichloromethane) at around ambient temperature.

Particular reduction approaches include the removal of oxygen atoms from particular functional groups or saturation (or partial saturation) of unsaturated compounds including aromatic or heteroaromatic rings. For example, primary alco-

hols can be generated from the corresponding ester or aldehyde by reduction, using a metal hydride (such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol). Alternatively, CH_2OH groups can be generated from the corresponding carboxylic acid by reduction, using a metal hydride (such as lithium aluminium hydride in a solvent such as tetrahydrofuran). In another example, a nitro group may be reduced to an amine by catalytic hydrogenation in the presence of a metal catalyst (such as palladium on a solid support such as carbon) in a solvent (such as an ether, for example tetrahydrofuran, or an alcohol, such as methanol), or by chemical reduction using a metal (such as zinc, tin or iron) in the presence of an acid (such as acetic acid or hydrochloric acid). In a further example an amine can be obtained by reduction of a nitrile, for example by catalytic hydrogenation in the presence of a metal catalyst (such as palladium on a solid support such as carbon), or Raney nickel in a solvent (such as tetrahydrofuran) and under suitable conditions (such as cooling to below room temperature, for example to −78° C., or heating, for example to reflux).

Salts of compounds of General Formula I can be prepared by the reaction of a compound of General Formula I with an appropriate acid or base in a suitable solvent, or mixture of solvents (such as an ether, for example, diethyl ether, or an alcohol, for example ethanol, or an aqueous solvent) using conventional procedures. Salts of compound of General Formula I can be exchanged for other salts by treatment using conventional ion-exchange chromatography procedures.

Where it is desired to obtain a particular enantiomer of a compound of General Formula I, this may be produced from a corresponding mixture of enantiomers by employing any suitable conventional procedure for resolving enantiomers. For example, diastereomeric derivatives (such as salts) can be produced by reaction of a mixture of enantiomers of a compound of General Formula I (such a racemate) and an appropriate chiral compound (such as a chiral base). The diastereomers can then be separated by any conventional means such as crystallisation, and the desired enantiomer recovered (such as by treatment with an acid in the instance where the diastereomer is a salt). Alternatively, a racemic mixture of esters can be resolved by kinetic hydrolysis using a variety of biocatalysts (for example, see Patel Steroselective Biocatalysts, Marcel Decker; New York 2000).

In another resolution process a racemate of compounds of General Formula I can be separated using chiral High Performance Liquid Chromatography. Alternatively, a particular enantiomer can be obtained by using an appropriate chiral intermediate in one of the processes described above. Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

II. Methods

Another aspect of the invention provides methods of modulating the activity of MetAP2. Such methods comprise exposing said receptor to a compound described herein. In some embodiments, the compound utilized by one or more of the foregoing methods is one of the generic, subgeneric, or specific compounds described herein, such as a compound of Formula I, Ia, Ib, Ic, Id, Ie, If, II, III or IV. The ability of compounds described herein to modulate or inhibit MetAP2 can be evaluated by procedures known in the art and/or described herein. Another aspect of the invention provides methods of treating a disease associated with expression or activity of MetAP2 in a patient. For example, a contemplated method includes administering a disclosed compound in an amount sufficient to establish inhibition of intracellular MetAP2 effective to increase thioredoxin production in the patient and to induce multi organ stimulation of anti-obesity processes in the subject, for example, by administering a disclosed compound in an amount insufficient to reduce angiogenesis in the patient.

In certain embodiments, the invention provides a method of treating and or ameliorating obesity in a patient by administering an effective amount of a disclosed compound. Also provided herein are methods for inducing weight loss in a patient in need thereof. Contemplated patients include not only humans, but other animals such as companion animals (e.g., dogs, cats).

Other contemplated methods of treatment include method of treating or ameliorating an obesity-related condition or co-morbidity, by administering a compound disclosed herein to a subject. For example, contemplated herein are methods for treating type 2 diabetes in a patient in need thereof.

Exemplary co-morbidities include cardiac disorders, endocrine disorders, respiratory disorders, hepatic disorders, skeletal disorders, psychiatric disorders, metabolic disorders, and reproductive disorders.

Exemplary cardiac disorders include hypertension, dyslipidemia, ischemic heart disease, cardiomyopathy, cardiac infarction, stroke, venous thromboembolic disease and pulmonary hypertension. Exemplary endocrine disorders include type 2 diabetes and latent autoimmune diabetes in adults. Exemplary respiratory disorders include obesity-hypoventilation syndrome, asthma, and obstructive sleep apnea. An exemplary hepatic disorder is nonalcoholic fatty liver disease. Exemplary skeletal disorders include back pain and osteoarthritis of weight-bearing joints. Exemplary metabolic disorders include Prader-Willi Syndrome and polycystic ovary syndrome. Exemplary reproductive disorders include sexual dysfunction, erectile dysfunction, infertility, obstetric complications, and fetal abnormalities. Exemplary psychiatric disorders include weight-associated depression and anxiety.

In particular, in certain embodiments, the invention provides a method of treating the above medical indications comprising administering to a subject in need thereof a therapeutically effective amount of a compound described herein, such as a compound of Formula I, Ia, Ib, Ic, Id, Ie, If, II, III or IV.

Obesity or reference to "overweight" refers to an excess of fat in proportion to lean body mass. Excess fat accumulation is associated with increase in size (hypertrophy) as well as number (hyperplasia) of adipose tissue cells. Obesity is variously measured in terms of absolute weight, weight:height ratio, distribution of subcutaneous fat, and societal and esthetic norms. A common measure of body fat is Body Mass Index (BMI). The BMI refers to the ratio of body weight (expressed in kilograms) to the square of height (expressed in meters). Body mass index may be accurately calculated using either of the formulas: weight (kg)/height^2 (m^2) (SI) or 703× weight (lb)/height^2 (in^2) (US).

In accordance with the U.S. Centers for Disease Control and Prevention (CDC), an overweight adult has a BMI of 25 kg/m^2 to 29.9 kg/m^2, and an obese adult has a BMI of 30 kg/m^2 or greater. A BMI of 40 kg/m^2 or greater is indicative of morbid obesity or extreme obesity. Obesity can also refer to patients with a waist circumference of about 102 cm for males and about 88 cm for females. For children, the definitions of overweight and obese take into account age and gender effects on body fat. Patients with differing genetic background may be considered "obese" at a level differing from the general guidelines, above.

The compounds of the present invention also are useful for reducing the risk of secondary outcomes of obesity, such as reducing the risk of left ventricular hypertrophy. Methods for treating patients at risk of obesity, such as those patients who are overweight, but not obese, e.g. with a BMI of between about 25 and 30 kg/m^2, are also contemplated. In certain embodiments, a patient is a human.

BMI does not account for the fact that excess adipose can occur selectively in different parts of the body, and development of adipose tissue can be more dangerous to health in some parts of the body rather than in other parts of the body. For example, "central obesity", typically associated with an "apple-shaped" body, results from excess adiposity especially in the abdominal region, including belly fat and visceral fat, and carries higher risk of co-morbidity than "peripheral obesity", which is typically associated with a "pear-shaped" body resulting from excess adiposity especially on the hips. Measurement of waist/hip circumference ratio (WHR) can be used as an indicator of central obesity. A minimum WHR indicative of central obesity has been variously set, and a centrally obese adult typically has a WHR of about 0.85 or greater if female and about 0.9 or greater if male.

Methods of determining whether a subject is overweight or obese that account for the ratio of excess adipose tissue to lean body mass involve obtaining a body composition of the subject. Body composition can be obtained by measuring the thickness of subcutaneous fat in multiple places on the body, such as the abdominal area, the subscapular region, arms, buttocks and thighs. These measurements are then used to estimate total body fat with a margin of error of approximately four percentage points. Another method is bioelectrical impedance analysis (BIA), which uses the resistance of electrical flow through the body to estimate body fat. Another method is using a large tank of water to measure body buoyancy. Increased body fat will result in greater buoyancy, while greater muscle mass will result in a tendency to sink.

In another aspect, the invention provides methods for treating an overweight or obese subject involving determining a level of at least one biomarker related to being overweight or obese in the subject, and administering an effective amount of a disclosed compound to achieve a target level in the subject. Exemplary biomarkers include body weight, Body Mass Index (BMI), Waist/Hip ratio WHR, plasma adipokines, and a combination of two or more thereof.

In certain embodiments, the compound utilized by one or more of the foregoing methods is one of the generic, subgeneric, or specific compounds described herein, such as a compound of Formula I, Ia, Ib, Ic, Id, Ie, If, II, III or IV.

The compounds of the invention may be administered to patients (animals and humans) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. It will be appreciated that the dose required for use in any particular application will vary from patient to patient, not only with the particular compound or composition selected, but also with the route of administration, the nature of the condition being treated, the age and condition of the patient, concurrent medication or special diets then being followed by the patient, and other factors which those skilled in the art will recognize, with the appropriate dosage ultimately being at the discretion of the attendant physician. For treating clinical conditions and diseases noted above, a compound of this invention may be administered orally, subcutaneously, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Parenteral administration may include subcutaneous injections, intravenous or intramuscular injections or infusion techniques.

Treatment can be continued for as long or as short a period as desired. The compositions may be administered on a regimen of, for example, one to four or more times per day. A suitable treatment period can be, for example, at least about one week, at least about two weeks, at least about one month, at least about six months, at least about 1 year, or indefinitely. A treatment period can terminate when a desired result, for example a weight loss target, is achieved. A treatment regimen can include a corrective phase, during which dose sufficient to provide reduction of weight is administered, and can be followed by a maintenance phase, during which a e.g. a lower dose sufficient to prevent weight gain is administered. A suitable maintenance dose is likely to be found in the lower parts of the dose ranges provided herein, but corrective and maintenance doses can readily be established for individual subjects by those of skill in the art without undue experimentation, based on the disclosure herein. Maintenance doses can be employed to maintain body weight in subjects whose body weight has been previously controlled by other means, including diet and exercise, bariatric procedures such as bypass or banding surgeries, or treatments employing other pharmacological agents.

III. Pharmaceutical Compositions and Kits

Another aspect of the invention provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with a pharmaceutically acceptable carrier. In particular, the present disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with one or more pharmaceutically acceptable carriers. These formulations include those suitable for oral, rectal, topical, buccal, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions may be formulated as a unit dose, and/or may be formulated for oral or subcutaneous administration.

Exemplary pharmaceutical compositions of this invention may be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more of the compound of the invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical carrier, e.g., conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g., water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Compositions and compounds of the present invention may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants

In another aspect, the invention provides enteral pharmaceutical formulations including a disclosed compound and an enteric material; and a pharmaceutically acceptable carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5. Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8,

of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about 8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal collophorium, and several commercially available enteric dispersion systems (e.g., Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable in vitro. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure would recognize that it is not comprehensive and that there are other enteric materials that would meet the objectives of the present invention.

Advantageously, the invention also provides kits for use by a e.g. a consumer in need of weight loss. Such kits include a suitable dosage form such as those described above and instructions describing the method of using such dosage form to mediate, reduce or prevent inflammation. The instructions would direct the consumer or medical personnel to administer the dosage form according to administration modes known to those skilled in the art. Such kits could advantageously be packaged and sold in single or multiple kit units. An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . . " etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a first compound can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

Also contemplated herein are methods and compositions that include a second active agent, or administering a second active agent. For example, in addition to being overweight or obese, a subject or patient can further have overweight- or obesity-related co-morbidities, i.e., diseases and other adverse health conditions associated with, exacerbated by, or precipitated by being overweight or obese. Contemplated herein are disclosed compounds in combination with at least one other agent that has previously been shown to treat these overweight- or obesity-related conditions.

For example, Type II diabetes has been associated with obesity. Certain complications of Type II diabetes, e.g., disability and premature death, can be prevented, ameliorated, or eliminated by sustained weight loss (Astrup, A. Pub Health Nutr (2001) 4:499-5 15). Agents administered to treat Type II diabetes include sulfonylureas (e.g., Chlorpropamide, Glipizide, Glyburide, Glimepiride); meglitinides (e.g., Repaglinide and Nateglinide); biguanides (e.g., Metformin); thiazolidinediones (Rosiglitazone, Troglitazone, and Pioglitazone); dipeptidylpeptidase-4 inhibitors (e.g., Sitagliptin, Vildagliptin, and Saxagliptin); glucagon-like peptide-1 mimetics (e.g., Exenatide and Liraglutide); and alpha-glucosidase inhibitors (e.g., Acarbose and Miglitol.

Cardiac disorders and conditions, for example hypertension, dyslipidemia, ischemic heart disease, cardiomyopathy, cardiac infarction, stroke, venous thromboembolic disease and pulmonary hypertension, have been linked to overweight or obesity. For example, hypertension has been linked to obesity because excess adipose tissue secretes substances that are acted on by the kidneys, resulting in hypertension. Additionally, with obesity there are generally higher amounts of insulin produced (because of the excess adipose tissue) and this excess insulin also elevates blood pressure. A major treatment option of hypertension is weight loss. Agents administered to treat hypertension include Chlorthalidone; Hydrochlorothiazide; Indapamide, Metolazone; loop diuretics (e.g., Bumetanide, Ethacrynic acid, Furosemide, Lasix, Torsemide); potassium-sparing agents (e.g., Amiloride hydrochloride, benzamil, Spironolactone, and Triamterene); peripheral agents (e.g., Reserpine); central alpha-agonists (e.g., Clonidine hydrochloride, Guanabenz acetate, Guanfacine hydrochloride, and Methyldopa); alpha-blockers (e.g., Doxazosin mesylate, Prazosin hydrochloride, and Terazosin hydrochloride); beta-blockers (e.g., Acebutolol, Atenolol, Betaxolol, Bisoprolol fumarate, Carteolol hydrochloride, Metoprolol tartrate, Metoprolol succinate, Nadolol, Penbutolol sulfate, Pindolol, Propranolol hydrochloride, and Timolol maleate); combined alpha- and beta-blockers (e.g., Carvedilol and Labetalol hydrochloride); direct vasodilators (e.g., Hydralazine hydrochloride and Minoxidil); calcium antagonists (e.g., Diltiazem hydrochloride and Verapamil hydrochloride); dihydropyridines (e.g., Amlodipine besylate, Felodipine, Isradipine, Nicardipine, Nifedipine, and Nisoldipine); ACE inhibitors (benazepril hydrochloride, Captopril, Enalapril maleate, Fosinopril sodium, Lisinopril, Moexipril, Quinapril hydrochloride, Ramipril, Trandolapril); Angiotensin II receptor blockers (e.g., Losartan potassium, Valsartan, and Irbesartan); Renin inhibitors (e.g., Aliskiren); and combinations thereof. These compounds are administered in regimens and at dosages known in the art.

Carr et al. (The Journal of Clinical Endocrinology & Metabolism (2004) Vol. 89, No. 6 2601-2607) discusses a link between being overweight or obese and dyslipidemia. Dyslipidemia is typically treated with statins. Statins, HMG-CoA reductase inhibitors, slow down production of cholesterol in a

subject and/or remove cholesterol buildup from arteries. Statins include mevastatin, lovastatin, pravastatin, simvastatin, velostatin, dihydrocompactin, fluvastatin, atorvastatin, dalvastatin, carvastatin, crilvastatin, bevastatin, cefvastatin, rosuvastatin, pitavastatin, and glenvastatin. These compounds are administered in regimens and at dosages known in the art. Eckel (Circulation (1997) 96:3248-3250) discusses a link between being overweight or obese and ischemic heart disease. Agents administered to treat ischemic heart disease include statins, nitrates (e.g., Isosorbide Dinitrate and Isosorbide Mononitrate), beta-blockers, and calcium channel antagonists. These compounds are administered in regimens and at dosages known in the art.

Wong et al. (Nature Clinical Practice Cardiovascular Medicine (2007) 4:436-443) discusses a link between being overweight or obese and cardiomyopathy. Agents administered to treat cardiomyopathy include inotropic agents (e.g., Digoxin), diuretics (e.g., Furosemide), ACE inhibitors, calcium antagonists, anti-arrhythmic agents (e.g., Sotolol, Amiodarone and Disopyramide), and beta-blockers. These compounds are administered in regimens and at dosages known in the art. Yusef et al. (Lancet (2005) 366(9497):1640-1649) discusses a link between being overweight or obese and cardiac infarction. Agents administered to treat cardiac infarction include ACE inhibitors, Angiotensin II receptor blockers, direct vasodilators, beta blockers, anti-arrhythmic agents and thrombolytic agents (e.g., Alteplase, Retaplase, Tenecteplase, Anistreplase, and Urokinase). These compounds are administered in regimens and at dosages known in the art.

Suk et al. (Stroke (2003) 34:1586-1592) discusses a link between being overweight or obese and strokes. Agents administered to treat strokes include anti-platelet agents (e.g., Aspirin, Clopidogrel, Dipyridamole, and Ticlopidine), anticoagulant agents (e.g., Heparin), and thrombolytic agents. Stein et al. (The American Journal of Medicine (2005) 18(9): 978-980) discusses a link between being overweight or obese and venous thromboembolic disease. Agents administered to treat venous thromboembolic disease include anti-platelet agents, anticoagulant agents, and thrombolytic agents. Sztrymf et al. (Rev Pneumol Clin (2002) 58(2):104-10) discusses a link between being overweight or obese and pulmonary hypertension. Agents administered to treat pulmonary hypertension include inotropic agents, anticoagulant agents, diuretics, potassium (e.g., K-dur), vasodilators (e.g., Nifedipine and Diltiazem), Bosentan, Epoprostenol, and Sildenafil. Respiratory disorders and conditions such as obesity-hypoventilation syndrome, asthma, and obstructive sleep apnea, have been linked to being overweight or obese. Elamin (*Chest* (2004) 125:1972-1974) discusses a link between being overweight or obese and asthma. Agents administered to treat asthma include bronchodilators, anti-inflammatory agents, leukotriene blockers, and anti-Ige agents. Particular asthma agents include Zafirlukast, Flunisolide, Triamcinolone, Beclomethasone, Terbutaline, Fluticasone, Formoterol, Beclomethasone, Salmeterol, Theophylline, and Xopenex.

Kessler et al. (Eur Respir J (1996) 9:787-794) discusses a link between being overweight or obese and obstructive sleep apnea. Agents administered to treat sleep apnea include Modafinil and amphetamines.

Hepatic disorders and conditions, such as nonalcoholic fatty liver disease, have been linked to being overweight or obese. Tolman et al. (Ther Clin Risk Manag (2007) 6:1153-1163) discusses a link between being overweight or obese and nonalcoholic fatty liver disease. Agents administered to treat nonalcoholic fatty liver disease include antioxidants (e.g., Vitamins E and C), insulin sensitizers (Metformin, Pioglitazone, Rosiglitazone, and Betaine), hepatoprotectants, and lipid-lowering agents.

Skeletal disorders and conditions, such as, back pain and osteoarthritis of weight-bearing joints, have been linked to being overweight or obese. van Saase (J Rheumatol (1988) 15(7):1152-1158) discusses a link between being overweight or obese and osteoarthritis of weight-bearing joints. Agents administered to treat osteoarthritis of weight-bearing joints include Acetaminophen, non-steroidal anti-inflammatory agents (e.g., Ibuprofen, Etodolac, Oxaprozin, Naproxen, Diclofenac, and Nabumetone), COX-2 inhibitors (e.g., Celecoxib), steroids, supplements (e.g. glucosamine and chondroitin sulfate), and artificial joint fluid.

Metabolic disorders and conditions, for example, Prader-Willi Syndrome and polycystic ovary syndrome, have been linked to being overweight or obese. Cassidy (Journal of Medical Genetics (1997) 34:917-923) discusses a link between being overweight or obese and Prader-Willi Syndrome. Agents administered to treat Prader-Willi Syndrome include human growth hormone (HGH), somatropin, and weight loss agents (e.g., Orlistat, Sibutramine, Methamphetamine, Ionamin, Phentermine, Bupropion, Diethylpropion, Phendimetrazine, Benzphetermine, and Topamax).

Hoeger (Obstetrics and Gynecology Clinics of North America (2001) 28(1):85-97) discusses a link between being overweight or obese and polycystic ovary syndrome. Agents administered to treat polycystic ovary syndrome include insulin-sensitizers, combinations of synthetic estrogen and progesterone, Spironolactone, Eflomithine, and Clomiphene. Reproductive disorders and conditions such as sexual dysfunction, erectile dysfunction, infertility, obstetric complications, and fetal abnormalities, have been linked to being overweight or obese. Larsen et al. (Int J Obes (Lond) (2007) 8:1189-1198) discusses a link between being overweight or obese and sexual dysfunction. Chung et al. (Eur Urol (1999) 36(1):68-70) discusses a link between being overweight or obese and erectile dysfunction. Agents administered to treat erectile dysfunction include phosphodiesterase inhibitors (e.g., Tadalafil, Sildenafil citrate, and Vardenafil), prostaglandin E analogs (e.g., Alprostadil), alkaloids (e.g., Yohimbine), and testosterone. Pasquali et al. (Hum Reprod (1997) 1:82-87) discusses a link between being overweight or obese and infertility. Agents administered to treat infertility include Clomiphene, Clomiphene citrate, Bromocriptine, Gonadotropin-releasing Hormone (GnRH), GnRH agonist, GnRH antagonist, Tamoxifen/nolvadex, gonadotropins, Human Chorionic Gonadotropin (HCG), Human Menopausal Gonadotropin (HmG), progesterone, recombinant follicle stimulating hormone (FSH), Urofollitropin, Heparin, Follitropin alfa, and Follitropin beta.

Weiss et al. (American Journal of Obstetrics and Gynecology (2004) 190(4):1091-1097) discusses a link between being overweight or obese and obstetric complications. Agents administered to treat obstetric complications include Bupivacaine hydrochloride, Dinoprostone PGE2, Meperidine HCl, Ferro-folic-500/iberet-folic-500, Meperidine, Methylergonovine maleate, Ropivacaine HCl, Nalbuphine HCl, Oxymorphone HCl, Oxytocin, Dinoprostone, Ritodrine, Scopolamine hydrobromide, Sufentanil citrate, and Oxytocic.

Psychiatric disorders and conditions, for example, weight-associated depression and anxiety, have been linked to being overweight or obese. Dixson et al. (Arch Intern Med (2003) 163:2058-2065) discusses a link between being overweight or obese and depression. Agents administered to treat depression include serotonin reuptake inhibitors (e.g., Fluoxetine,

Escitalopram, Citalopram, Paroxetine, Sertraline, and Venlafaxine); tricyclic antidepressants (e.g., Amitriptyline, Amoxapine, Clomipramine, Desipramine, Dosulepin hydrochloride, Doxepin, Imipramine, Iprindole, Lofepramine, Nortriptyline, Opipramol, Protriptyline, and Trimipramine); monoamine oxidase inhibitors (e.g., Isocarboxazid, Moclobemide, Phenelzine, Tranylcypromine, Selegiline, Rasagiline, Nialamide, Iproniazid, Iproclozide, Toloxatone, Linezolid, Dienolide kavapyrone desmethoxyyangonin, and Dextroamphetamine); psychostimulants (e.g., Amphetamine, Methamphetamine, Methylphenidate, and Arecoline); antipsychotics (e.g., Butyrophenones, Phenothiazines, Thioxanthenes, Clozapine, Olanzapine, Risperidone, Quetiapine, Ziprasidone, Amisulpride, Paliperidone, Symbyax, Tetrabenazine, and Cannabidiol); and mood stabilizers (e.g., Lithium carbonate, Valproic acid, Divalproex sodium, Sodium valproate, Lamotrigine, Carbamazepine, Gabapentin, Oxcarbazepine, and Topiramate).

Simon et al. (Archives of General Psychiatry (2006) 63(7): 824-830) discusses a link between being overweight or obese and anxiety. Agents administered to treat anxiety include serotonin reuptake inhibitors, mood stabilizers, benzodiazepines (e.g., Alprazolam, Clonazepam, Diazepam, and Lorazepam), tricyclic antidepressants, monoamine oxidase inhibitors, and beta-blockers.

Another aspect of the invention provides methods for facilitating and maintaining weight loss in a subject involving administering to the subject an amount of a disclosed compound effective to result in weight loss in the subject; and administering a therapeutically effective amount of a different weight loss agent to maintain a reduced weight in the subject. Weight loss agents include serotonin and noradrenergic re-uptake inhibitors; noradrenergic re-uptake inhibitors; selective serotonin re-uptake inhibitors; and intestinal lipase inhibitors. Particular weight loss agents include orlistat, sibutramine, methamphetamine, ionamin, phentermine, bupropion, diethylpropion, phendimetrazine, benzphetermine, bromocriptine, lorcaserin, topiramate, or agents acting to modulate food intake by blocking ghrelin action, inhibiting diacylglycerol acyltransferase 1 (DGAT1) activity, inhibiting stearoyl CoA desaturase 1 (SCD1) activity, inhibiting neuropeptide Y receptor 1 function, activating neuropeptide Y receptor 2 or 4 function, or inhibiting activity of sodium-glucose cotransporters 1 or 2. These compounds are administered in regimens and at dosages known in the art.

EXAMPLES

The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials.

At least some of the compounds identified as "Intermediates" herein are contemplated as compounds of the invention.

^{1}H NMR spectra were recorded at ambient temperature using a Varian Unity Inova (400 MHz) spectrometer with a triple resonance 5 mm probe for Example compounds, and either a Bruker Avance DRX (400 MHz) spectrometer or a Bruker Avance DPX (300 MHz) spectrometer for Intermediate compounds. Chemical shifts are expressed in ppm relative to tetramethylsilane. The following abbreviations have been used: br=broad signal, s=singlet, d=doublet, dd=double doublet, ddd=double double doublet, dt=double triplet, t=triplet, td=triple doublet, q=quartet, m=multiplet.

Mass Spectrometry (LCMS) experiments to determine retention times and associated mass ions were performed using the following methods:

Method A: Experiments were performed on a Waters ZMD LC quadrapole mass spectrometer linked to a Waters 1525 LC system with a diode array detector. The spectrometer has an electrospray source operating in positive and negative ion mode. Additional detection was achieved using a Sedex 85 evaporative light scattering detector. LC was carried out using a Luna 3 micron 30×4.6 mm C18 column and a 2 mL/minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.5 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 minutes. The final solvent system was held constant for a further 1 minute.

Method B: Experiments were performed on a Waters V G Platform quadrupole spectrometer linked to a Hewlett Packard 1050 LC system with a diode array detector. The spectrometer has an electrospray source operating in positive and negative ion mode. Additional detection was achieved using a Sedex 85 evaporative light scattering detector. LC was carried out using a Luna 3 micron 30×4.6 mm C18 column and a 2 mL/minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.3 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 minutes. The final solvent system was held constant for a further 1 minute.

Method C: Experiments were performed on a Waters Micromass ZQ2000 quadrapole mass spectrometer linked to a Waters Acquity UPLC system with a PDA UV detector. The spectrometer has an electrospray source operating in positive and negative ion mode. LC was carried out using an Acquity BEH 1.7 micron C18 column, an Acquity BEH Shield 1.7 micron RP18 column or an Acquity HSST 1.8 micron column. Each column has dimensions of 100×2.1 mm and was maintained at 40° C. with a flow rate of 0.4 mL/minute. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.4 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 6 minutes. The final solvent system was held constant for a further 0.8 minutes.

Method D: Experiments were performed on a Shimadzu LCMS-2020 spectrometer with an electrospray source operating in positive ion mode. LC was carried out using a Shimadzu Shim-pack XR-ODS 2.2 micron 50×3.0 mm column. The initial solvent system was 95% water containing 0.05% trifluoroacetic acid (solvent A) and 5% acetonitrile (solvent B) for the first 0.01 minute then a gradient up to 100% solvent B over the next 1.3 minutes. The final solvent syt=stem was held constant for a further 1 minute.

Method E: Experiments were performed on a Waters ZMD LC quadrapole mass spectrometer linked to a Hewlett Packard HD 1100 system with a diode array detector. The spectrometer has an electrospray source operating in positive and

negative ion mode. LC was carried out using a Luna 3 micron 30×4.6 mm C18 column and a 2 mL/minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.5 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 minutes. The final solvent system was held constant for a further 1 minute.

Method F: Experiments were performed on a Waters V G Platform quadrupole spectrometer linked to a Hewlett Packard 1050 LC system with a diode array detector. The spectrometer has an electrospray source operating in positive and negative ion mode. Additional detection was achieved using a Sedex 85 evaporative light scattering detector. LC was carried out using a Luna 3 micron 30×4.6 mm C18 column and a 2 mL/minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first 0.3 minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 minutes. The final solvent system was held constant for a further 1 minute. Microwave experiments were carried out using a Biotage Initiator™, which uses a single-mode resonator and dynamic field tuning. Temperatures from 40-250° C. can be achieved, and pressures of up to 20 bars can be reached. A facility exists to apply air cooling during the irradiation.

Preparative HPLC purification was carried out using either a C18-reverse-phase column from Genesis (C18) or a C6-phenyl column from Phenomenex (C6-phenyl) (100×22.5 mm i.d. with 7 micron particle size, UV detection at 230 or 254 nm, flow 5-15 mL/min), eluting with gradients from 100-0 to 0-100% water/acetonitrile or water/methanol containing 0.1% formic acid. Fractions containing the required product (identified by LCMS analysis) were pooled, the organic fraction removed by evaporation, and the remaining aqueous fraction lyophilised, to give the product.

Compounds which required column chromatography were purified manually or fully automatically using either a Biotage SP1™ Flash Purification system with Touch Logic Control™ or a Combiflash Companion® with pre-packed silica gel Isolute® SPE cartridge, Biotage SNAP cartridge or Redisep® Rf cartridge respectively.

Compounds have been named using Autonom2000 within ISISDraw.

Abbreviations

DCM Dichloromethane

IMS Industrial methylated spirits

DMF N,N-Dimethylformamide

DMAP 4-Dimethylaminopyridine

THF Tetrahydrofuran

DMSO Dimethylsulfoxide

NMP N-methylpyrrolidinone

DCE 1,2-Dichloroethane

HATU 7-Azabenzotriazol-1-yl-N,N,N',N',tetramethyluronium hexafluorophosphate

EDAC N-(3-Dimethylaminopropyl)-N'ethylcarbodiimide hydrochloride

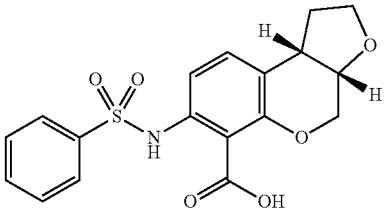
IMS Industrial methylated spirit

NMM N-methylmorpholine

DBU 1,8-Diazabicyclo[5.4.0]undec-7-ene

Example 1

Cis-(3aRS,9bRS)-7-(Benzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid



Mixture of cis enantiomers

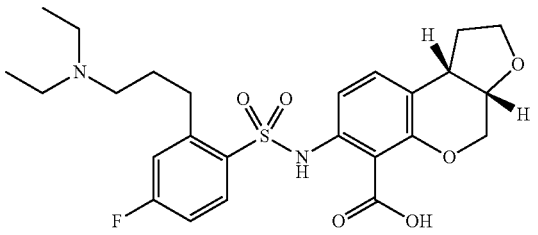
Lithium hydroxide (0.048 g) was added to a solution of methyl cis-(3aRS,9bRS)-7-(benzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (Intermediate 1, 0.08 g) in a mixture of dioxane (10 mL) and water (5 mL) and the resultant mixture was irradiated in the microwave at 110° C. with air cooling for 20 minutes. Further lithium hydroxide (0.2 g) was added and the mixture was irradiated in the microwave at 110° C. with air cooling for a total of 80 minutes. After cooling, the solution was acidified by addition of aqueous formic acid solution (10%) and the resultant mixture was extracted with ethyl acetate, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness. The residue was dissolved in a mixture of methanol (10 mL) and water (5 mL) and treated with lithium hydroxide (0.2 g) then irradiated in the microwave at 110° C. with air cooling for 40 minutes. After cooling, the solution was acidified by addition of formic acid (10%) and the resultant mixture was extracted with ethyl acetate, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by preparative HPLC (C18) eluting with a mixture of acetonitrile and water, containing 0.1% formic acid, with a gradient of 30-50% to give cis-(3aRS,9bRS)-7-(benzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid (0.019 g) as a white solid.

^{1}H NMR (CD_3OD) δ: 7.71 (2H, d), 7.54 (1H, t), 7.44 (2H, t), 7.24 (1H, d), 7.12 (1H, d), 4.24 (1H, m), 4.09 (1H, dd), 3.92 (1H, dd), 3.8-3.65 (2H, m), 3.47 (1H, m), 2.45 (1H, m), 1.83 (1H, m).

LCMS (Method C) r/t 3.79 (M−H) 374.

Example 2

Cis-(3aRS,9bRS)-7-[2-(3-Diethylaminopropyl)-4-fluorobenzenesulfonyl-amino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid



Mixture of cis enantiomers

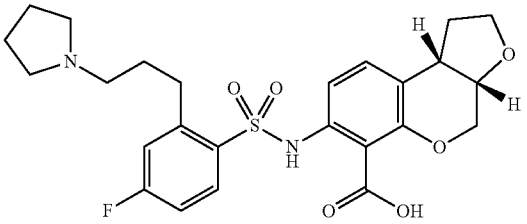
A solution of 7-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-4H-furo[2,3-c]chromene-6-carboxylic acid (Intermediate 8, 0.1 g) in a mixture of IMS (2 mL) and glacial acetic acid (3 mL) was treated, under an atmosphere of nitrogen, with palladium hydroxide on carbon (10%, 0.02 g). The nitrogen was replaced by hydrogen and the mixture was stirred under an atmosphere of hydrogen for 100 minutes. The mixture was filtered through Celite and the filtrate was evaporated to dryness. The residue was dissolved in toluene and the solution was re-evaporated. The residue was triturated with ether and the solid was collected by filtration and purified by preparative HPLC (C6-phenyl) eluting with a mixture of acetonitrile and water, containing 0.1% formic acid, with a gradient of 20-40% to give cis-(3aRS, 9bRS)-7-[2-(3-diethylaminopropyl-4-fluorobenzenesulfonyl-amino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid (0.1 g) as a white solid.

^{1}H NMR (CD_3OD) δ: 7.94 (1H, dd), 7.18 (1H, d), 7.17 (1H, m), 7.06 (1H, d), 6.99 (1H, dt), 4.21 (1H, m), 3.98 (1H, dd), 3.88 (1H, dd), 3.72 (2H, m), 3.42 (1H, m), 3.23 (6H, m), 3.10 (2H, m), 2.42 (1H, m), 1.98 (2H, m), 1.81 (1H, m), 1.31 (6H, t).

LCMS (Method C) r/t 3.10 (M+H) 507.

Example 3

Cis-(3aRS,9bRS)-7-[2-(3-{Pyrrolidin-1-yl}propyl)-4-fluorobenzene-sulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid



Mixture of cis enantiomers

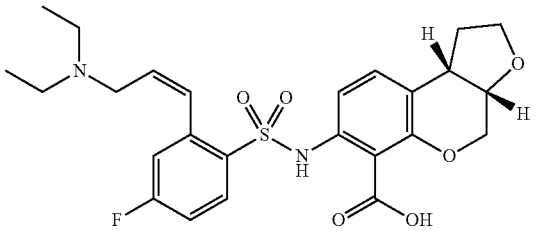
Lithium hydroxide (0.028 g) was added to a solution of methyl cis-(3aRS,9bRS)-7-[2-(3-{pyrrolidin-1-yl}propyl)-4-fluorobenzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (Intermediate 14, 0.06 g) in dioxane (2 mL) and water (1 mL) and the mixture was stirred and heated at 80° C. for 8 hours. After cooling, the mixture was acidified by addition of aqueous formic acid solution (10%) and extracted with DCM. The organic layer was dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of ammonia in methanol (2M) and DCM with a gradient of 1-10%. The isolated solid was triturated with a mixture of ether and cyclohexane (50%) and the solid was collected by filtration. The solid was purified by preparative HPLC (C18) eluting with a mixture of acetonitrile and water, containing 0.1% formic acid, with a gradient of 10-95%. The isolated product was triturated with ether and the solid was collected by filtration to give cis-(3aRS,9bRS)-7-[2-(3-{pyrrolidin-1-yl}propyl)-4-fluorobenzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid (0.006 g) as a white solid.

^{1}H NMR (CD_3OD) δ: 7.93 (1H, dd), 7.21 (1H, d), 7.14 (1H, dd), 7.08 (1H, d), 6.99 (1H, dt), 4.21 (1H, m), 3.98 (1H, dd), 3.88 (1H, dd), 3.72 (2H, m), 3.43 (2H, m), 3.30 (4H, m), 3.13 (3H, m), 2.42 (1H, m), 2.07 (4H, m), 2.0 (2H, m), 1.81 (1H, m).

LCMS (Method C) r/t 3.11 (M+H) 505.

Example 4

Cis-(3aRS,9bRS)-7-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluoro-benzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid



Mixture of cis enantiomers

Prepared by proceeding in a similar manner to Example 3, starting from methyl cis-(3aRS,9bRS)-7-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (Intermediate 17) and heating at 80° C. overnight.

^{1}H NMR (DMSO-d_6) δ: 7.65 (1H, dd), 7.30 (1H, d), 7.19 (2H, m), 7.02 (1H, d), 6.92 (1H, d), 6.10 (1H, m), 4.09 (1H, m), 3.82-3.64 (4H, m), 3.63-3.30 (3H, m), 3.03 (4H, q), 2.35 (1H, m), 1.68 (1H, m), 1.07 (6H, t).

LCMS (Method C) r/t 3.05 (M+H) 505.

Examples 5 and 6

Separation of Enantiomers from Example 4

Sample from Example 4 was subjected to chiral separation using a ChiralPak IC column, 4.6 mm×250 mm, particle size 5 micron. Injection solvent DCE:absolute ethanol 1:1, injection concentration 1 mg/100 μL, injection volume 120 μL. Eluting solvent absolute ethanol, flow rate 0.55 mL/minute, temperature 21° C.

Example 5

First Eluting Enantiomer: Retention Time on Above Column: 34.96 Minutes, 93% De

^{1}H NMR (DMSO-d_6) δ: 7.64 (1H, dd), 7.29 (1H, d), 7.18 (2H, m), 7.01 (1H, d), 6.92 (1H, d), 6.08 (1H, m), 4.09 (1H, m), 3.75 (2H, m), 3.59 (2H, m), 3.33 (3H, m), 3.03 (4H, br), 2.34 (1H, m), 1.68 (1H, m), 1.06 (6H, t).

LCMS (Method C) r/t 3.07 (M+H) 505.

Example 6

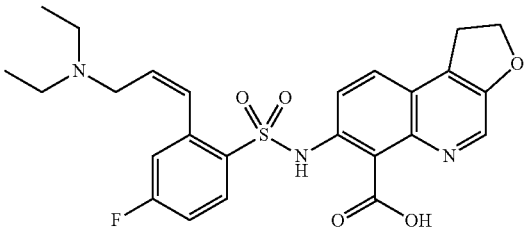
Second Eluting Enantiomer: Retention Time on Above Column 40.97 Minutes, 65% de

^{1}H NMR (DMSO-d_6) δ: 7.64 (1H, dd), 7.29 (1H, d), 7.18 (2H, m), 7.01 (1H, d), 6.92 (1H, d), 6.08 (1H, m), 4.09 (1H, m), 3.75 (2H, m), 3.59 (2H, m), 3.33 (3H, m), 3.03 (4H, br), 2.34 (1H, m), 1.68 (1H, m), 1.06 (6H, t).

LCMS (Method C) r/t 3.06 (M+H) 505.

Example 7

7-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,2-dihydrofuro[2,3-c]quinoline-6-carboxylic acid formate salt



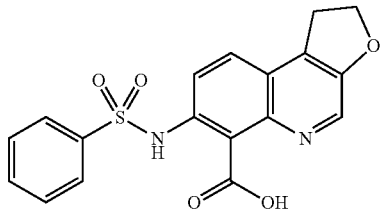
Prepared by proceeding in a similar manner to Example 1, starting from methyl 7-[N-{2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonyl}-N-(methoxy-carbonyl) amino]-1,2-dihydrofuro[2,3-c]quinoline-6-carboxylate (Intermediate 20) as a yellow solid.

^{1}H NMR (CD_3OD) δ: 8.50 (1H, s), 8.47 (2H, s), 7.96 (1H, m), 7.91 (1H, d), 7.79 (1H, d), 7.45 (1H, d), 7.11 (2H, m), 6.13 (1H, m), 3.79 (2H, d), 3.59 (2H, t), 3.10 (6H, m), 1.16 (6H, m).

LCMS (Method C) r/t 2.84 (M+H) 500.

Example 8

7-(Benzenesulfonylamino)-1,2-dihydrofuro[2,3-c] quinoline-6-carboxylic acid formate salt



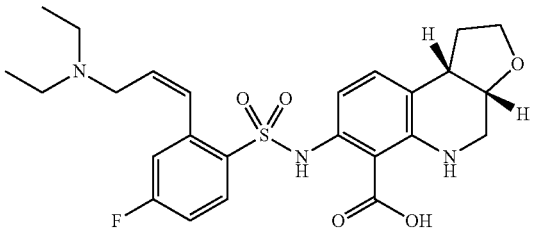
Prepared by proceeding in a similar manner to Example 1, starting from methyl 7-(benzenesulfonylamino)-1,2-dihydrofuro[2,3-c]quinoline-6-carboxylate (Intermediate 26).

^{1}H NMR (DMSO-d_6) δ: 8.54 (1H, s), 8.25 (1H, s), 7.78 (3H, m), 7.66 (1H, d), 7.44 (3H, m), 4.69 (2H, t), 3.46 (2H, t).

LCMS (Method C) r/t 3.66 (M+H) 371.

Example 9

Cis-(3aRS,9bRS)-7-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-6-carboxylic acid



Mixture of cis enantiomers

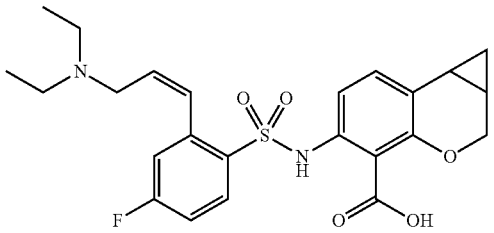
Lithium hydroxide (0.09 g) was added to a solution of methyl cis-(3aRS,9bRS)-5-acetyl-7-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-6-carboxylate (Intermediate 27, 0.06 g) in a mixture of dioxane (5 mL) and water (1 mL) and the mixture was stirred and heated at 80° C. overnight. The mixture was then irradiated in the microwave at 150° C. for 30 minutes and then at 180° C. for 30 minutes. After cooling, the mixture was filtered and the filtrate was acidified by addition of formic acid (1 mL) and then evaporated to dryness. The residue was purified by preparative HPLC (C18) eluting with a mixture of acetonitrile and water, containing 0.1% formic acid, with a gradient of 10-98%. The isolated product was dissolved in DCM and evaporated to dryness then dissolved in ether and evaporated to dryness to give cis-(3aRS,9bRS)-7-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,2,3a,4,5,9b-hexahydrofuro [2,3-c]quinoline-6-carboxylic acid (0.005 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 8.54 (1H, br s), 7.99 (1H, br s), 7.48 (1H, d), 7.04 (1H, m), 6.90 (1H, d), 6.76 (1H, d), 6.62 (1H, m), 6.11 (1H, m), 4.17 (1H, m), 3.82 (1H, m), 3.78-3.59 (2H, m), 3.32-3.10 (4H, m), 3.04-2.86 (3H, m), 2.35 (1H, m), 1.79 (1H, m), 1.15 (6H, t).

LCMS (Method C) r/t 3.31 (M+H) 504

Example 10

(1aRS,7bSR)-5-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



Methyl (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 40, 0.185 g) and lithium hydroxide monohydrate (0.159 g) were suspended in dioxane (4 mL) and water (1 mL). The reaction mixture was irradiated in the microwave at 135° C. for 30 minutes. After cooling, the mixture was acidified to pH4 with formic acid, then ethanol and toluene were added and the mixture concentrated in vacuo. The residue was triturated with a mixture of methanol and DCM (10%) and the solid was filtered off and washed with a mixture of methanol and DCM. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-8%. The resultant product was triturated with ethyl acetate and dried in vacuo at 50° C. to give (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.066 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.64 (1H, dd), 7.35 (1H, d), 7.27-7.19 (2H, m), 7.10 (1H, d), 6.93 (1H, d), 6.20-6.10 (1H, m), 4.17 (1H, d), 3.76 (2H, br, s), 3.57 (1H, d), 3.10 (4H, br, q), 1.92 (1H, td), 1.75-1.69 (1H, m), 1.13 (6H, t), 0.94 (1H, td), 0.74 (1H, m).

LCMS (Method C) r/t 3.32 (M+H) 475

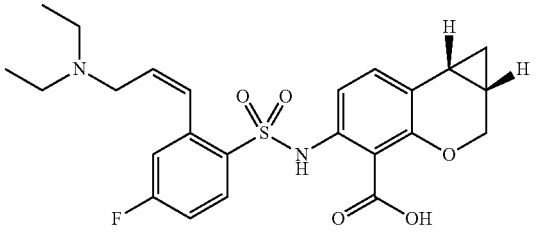
Examples 11 and 12

Separation of Enantiomers from Example 10

Sample from Example 10 was subjected to chiral separation using a ChiralPak IC column, 10 mm×250 mm, particle size 5 micron. Eluting solvent tert-butyl methyl ether:isopropanol:DCM (16:20:64).

Example 11

First eluting enantiomer: r/t on analytical column (4.6 mm×250 mm): 21.8 minutes>99% ee: (1aS, 7bR)-5-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid

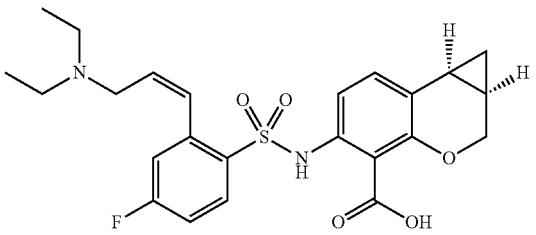


^{1}H NMR ($CDCl_3$) δ: 7.63 (1H, d), 7.43 (1H, m), 7.15-7.08 (2H, m), 6.85 (1H, dt), 6.72 (1H, dd), 5.93 (1H, m), 4.27 (1H, d), 3.98 (1H, br m), 3.68 (1H, m), 3.58 (1H, br), 3.27-3.06 (4H, m), 1.87 (1H, m), 1.63 (1H, m), 1.23 (6H, t), 1.04 (1H, m), 0.91 (1H, m).

LCMS (Method C) r/t 3.30 (M+H) 475

Example 12

Second eluting enantiomer: r/t on analytical column (4.6 mm×250 mm): 27.5 minutes, >99% ee: (1aR, 7bS)-5-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



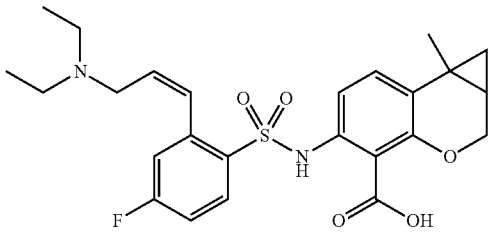
^{1}H NMR $CDCl_3$) δ: 7.63 (1H, d), 7.43 (1H, m), 7.15-7.08 (2H, m), 6.85 (1H, dt), 6.72 (1H, dd), 5.93 (1H, m), 4.27 (1H, d), 3.98 (1H, br m), 3.68 (1H, m), 3.58 (1H, br), 3.27-3.06 (4H, m), 1.87 (1H, m), 1.63 (1H, m), 1.23 (6H, t), 1.04 (1H, m), 0.91 (1H, m).

LCMS (Method C) r/t 3.32 (M+H) 475.

Absolute configuration of Examples 11 and 12 determined by X-ray crystal analysis of Example 12 with MetAP2.

Example 13

(1aRS,7bSR)-5-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



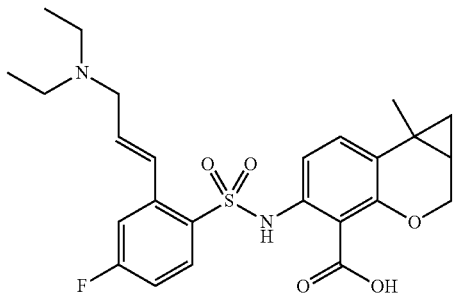
Prepared by proceeding in a similar manner to Example 3, starting from methyl (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermeidate 48).

^{1}H NMR ($CDCl_3$) δ: 9.8-9.2 (1H, br s), 7.65 (1H, d), 7.39 (1H, m), 7.24 (1H, d), 7.18 (1H, d), 6.83 (1H, dt), 6.72 (1H, dd), 5.91 (1H, m), 4.21 (1H, d), 3.98 (1H, br t), 3.71 (1H, d), 3.61 (1H, br s), 3.28-3.06 (4H, m), 1.41 (3H, s), 1.37 (1H, m), 1.24 (6H, t), 1.14 (1H, t), 0.74 (1H, dd).

LCMS (Method C) r/t 3.55 (M+H) 489.

Example 14

(1aRS,7bSR)-5-[2-((E)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



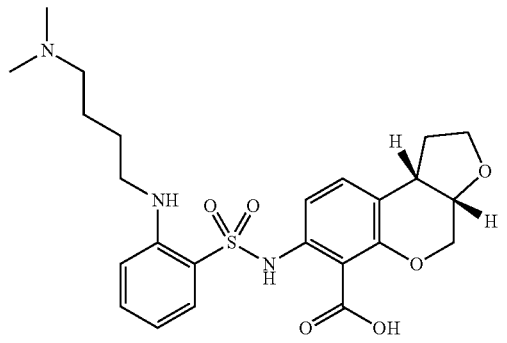
Isolated as a minor by-product by preparative HPLC from the preparation of Example 13.

^{1}H NMR ($CDCl_3$) δ: 11.9 (1H, br s), 7.93 (1H, dd), 7.70 (1H, d), 7.25 (1H, d), 7.10 (1H, d), 7.06 (1H, dd), 6.90 (1H, dt), 6.19 (1H, m), 4.23 (1H, d), 3.76 (1H, d), 3.68 (2H, m), 3.29 (4H, q), 1.36 (6H, t), 1.35 (3H, s), 1.31 (1H, m), 1.10 (1H, t), 1.67 (1H, dd).

LCMS (Method C) r/t 3.66 (M+H) 489.

Example 15

Cis-(3aRS,9bRS)-7-[2-(4-dimethylaminobutylamino)benzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid



Mixture of cis enantiomers

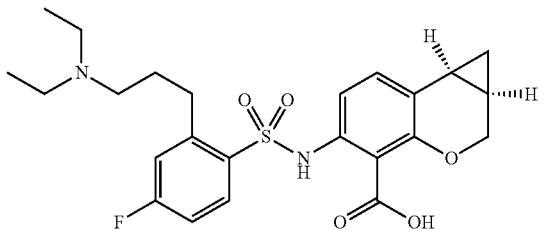
4-Dimethylaminobutylamine (0.348 g) and triethylamine (0.2 ml) were added to a suspension of cis-(3aRS,9bRS)-7-(2-fluorobenzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid (Intermediate 57, 0.15 g) in acetonitrile (1.5 mL) and the mixture was heated at 130° C. in a sealed tube for 36 hours. The mixture was then diluted with water (2 mL) and the solution was purified by preparative HPLC (C6-phenyl) eluting with a mixture of methanol and water, containing 0.1% formic acid, with a gradient of 5-98%. The isolated product was further purified by chromatography on silica eluting with a mixture of methanol and DCM with a gradient of 0-15% to give cis-(3aRS,9bRS)-7-[2-(4-dimethylaminobutylamino)-benzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid (0.062 g) as a glass foam.

^{1}H NMR ($CDCl_3$) δ: 11.21 (1H, br s), 7.72 (1H, dd), 7.37 (1H, d), 7.26 (1H, m), 7.02 (1H, d), 6.59 (1H, d), 6.56 (1H, t), 5.85 (1H, t), 4.29 (1H, dt), 4.05 (1H, dd), 3.85 (1H, m), 3.77 (2H, m), 3.34 (1H, q), 3.21 (2H, m), 2.98 (2H, t), 2.80 (6H, s), 2.41 (1H, m), 2.05 (1H, m), 1.83 (1H, m), 1.71 (2H, m).

LCMS (Method C) r/t 3.18 (M+H) 490

Example 16

(1aR,7bS)-5-[2-(3-Diethylaminopropyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



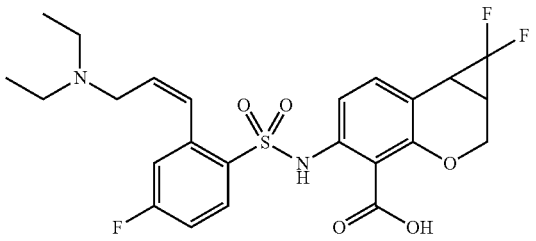
Prepared by proceeding in a similar manner to Example 2, starting from (1aR,7bS)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]-chromene-4-carboxylic acid (Example 12)

^{1}H NMR ($CDCl_3$) δ: 7.81 (1H, dd), 7.31 (1H, d), 7.07 (1H, d), 6.82 (2H, m), 4.32 (1H, d), 3.74 (1H, d), 3.42-3.32 (1H, m), 3.18 (4H, m), 3.14-2.94 (3H, m), 2.00 (2H, m), 1.84 (1H, m), 1.62 (1H, m), 1.31 (6H, t), 1.04 (1H, m), 0.88 (1H, m).

LCMS (Method C) r/t 3.36 (M+H) 477.

Example 17

(1aRS,7bSR)-5-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



Prepared by proceeding in a similar manner to Example 10, starting from methyl (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 59) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 10.0-9.6 (1H, br s), 7.64 (1H, d), 7.47 (1H, dd), 7.21 (1H, d), 7.13 (1H, d), 6.87 (1H, dt), 6.73 (1H, dd), 5.95 (1H, m), 4.28 (1H, d), 3.96 (1H, m), 3.92-3.79 (1H, br s), 3.78-3.67 (1H, br s), 3.17 (4H, q), 2.64 (1H, t), 2.23 (1H, m), 1.24 (6H, t).

LCMS (Method C) r/t 3.38 (M+H) 511.

Examples 18 and 19

Separation of Enantiomers from Example 17

Sample from Example 17 was subjected to chiral separation using a ChiralPak IA column, 20 mm×250 mm, particle size 5 micron. Eluting solvent methanol:ethanol:heptane (12.5:12.5:75).

Example 18

First eluting enantiomer: r/t on analytical column (4.6 mm×250 mm): 14.7 minutes>95% ee

^{1}H NMR (DMSO-d_6) δ: 7.83 (1H, t), 7.27-7.17 (3H, m), 7.09 (1H, d), 6.85 (1H, d), 5.98 (1H, m), 4.27 (1H, d), 3.76 (1H, m), 3.56 (1H, t), 2.90 (1H, t), 2.85 (1H, t), 2.77 (4H, br s), 2.55 (1H, s), 0.97 (6H, br t).

LCMS (Method C) r/t 3.39 (M+H) 511

Example 19

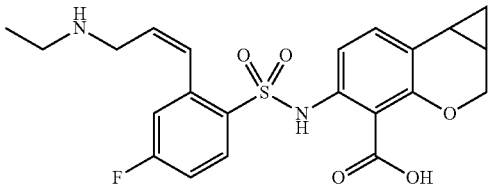
Second eluting enantiomer: r/t on analytical column 19.0 minutes, >95% ee

^{1}H NMR (DMSO-d_6) δ: 7.72 (1H, dd), 7.36 (1H, d), 7.26 (1H, dt), 7.21 (1H, dd), 7.18 (1H, d), 6.99 (1H, d), 6.13 (1H, m), 4.29 (1H, d), 3.87-3.70 (3H, m), 3.10 (4H, m), 2.96 (1H, t), 2.56 (1H, m), 1.11 (6H, t).

LCMS (Method C) r/t 3.39 (M+H) 511.

Example 20

(1aRS,7bSR)-5-[2((Z)-3-Ethylaminoprop-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid



A mixture of methyl (1aRS,7bSR)-5-[2((Z)-3-ethylamino-prop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 63, 0.09 g) and lithium hydroxide monohydrate (0.047 g) in a mixture of dioxane (10 mL) and water (5 mL) was stirred and heated at 120° C. for 32 hours. After cooling, the mixture was concentrated under vacuum and the residue was acidified to pH4 with formic acid. The resultant solid was collected by filtration and washed with water to give (1aRS,7bSR)-5-[2((Z)-3-ethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (0.029 g) as a grey solid.

^{1}H NMR (DMSO-d_6) δ: 10.4-9.95 (1H, br s), 7.51 (1H, dd), 7.21 (1H, d), 7.17 (1H, dt), 7.11 (1H, dd), 7.07 (1H, d), 6.99 (1H, d), 5.93 (1H, m), 4.11 (1H, d), 3.60 (2H, m), 3.51 (1H, d), 2.92 (2H, q), 1.87 (1H, m), 1.67 (1H, m), 1.12 (3H, t), 0.89 (1H, m), 0.69 (1H, m).

LCMS (Method C) r/t 3.32 (M+H) 447.

Examples 21 and 22

Separation of Enantiomers from Example 20

Sample from Example 20 was subjected to chiral separation using a ChiralPak IC column, 10 mm×250 mm, particle size 5 micron. Eluting solvent tert-butyl methyl ether:isopropanol:DCM (15:20:65).

Example 21

First eluting enantiomer: r/t on analytical column (4.6 mm×250 mm): 14.3 minutes>99% ee

^{1}H NMR (DMSO-d_6) δ: 10.16 (2H, br s), 7.56 (1H, dd), 7.26 (1H, d), 7.22 (1H, dt), 7.17 (1H, dd), 7.12 (1H, d), 7.05 (1H, d), 5.99 (1H, m), 4.16 (1H, d), 3.65 (2H, m), 3.57 (1H, d), 2.98 (2H, q), 1.93 (1H, m), 1.73 (1H, m), 1.17 (3H, t), 0.94 (1H, m), 0.78 (1H, q).

LCMS (Method C) r/t 3.27 (M+H) 447.

Example 22

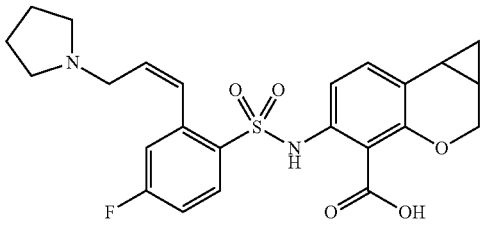
Second eluting enantiomer: r/t on analytical column 20.6 minutes, >99% ee

^{1}H NMR (DMSO-d_6): δ: 10.16 (2H, br s), 7.56 (1H, dd), 7.26 (1H, d), 7.22 (1H, dt), 7.17 (1H, dd), 7.12 (1H, d), 7.05 (1H, d), 5.99 (1H, m), 4.16 (1H, d), 3.65 (2H, m), 3.57 (1H, d), 2.98 (2H, q), 1.93 (1H, dt), 1.73 (1H, m), 1.17 (3H, t), 0.94 (1H, dt), 0.75 (1H, q).

LCMS (Method C) r/t 3.26 (M+H) 447.

Example 23

(1aRS,7bSR)-5-{2[(Z)-3-(Pyrrolidin-1-yl)prop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



Prepared by proceeding in a similar manner to Example 20, starting from methyl (1aRS,7bSR)-5-{2[(Z)-3-(pyrrolidin-1-yl)prop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 66) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 12.2-11.6 (1H, br s), 7.49 (1H, dd), 7.30 (1H, d), 7.21-7.12 (2H, m), 7.09 (1H, m), 6.97 (1H, d), 6.10 (1H, m), 4.12 (1H, d), 3.80 (2H, d), 3.51 (1H, d), 3.28 (4H, m), 1.89 (1H, m), 1.85 (4H, m), 1.68 (1H, m), 0.90 (1H, m), 0.69 (1H, m).

LCMS (Method C) r/t 3.39 (M+H) 473

Examples 24 and 25

Separation of Enantiomers from Example 23

Sample from Example 23 was subjected to chiral separation using a ChiralPak IC column, 10 mm×250 mm, particle size 5 micron. Eluting solvent tert-butyl methyl ether:ethanol (75:25).

Example 24

First eluting enantiomer: r/t on analytical column (4.6 mm×250 mm): 17.5 minutes>99% ee

^{1}H NMR (DMSO-d_6) δ: 7.55 (1H, dd), 7.35 (1H, d), 7.22 (2H, m), 7.14 (1H, d), 7.02 (1H, d), 6.14 (1H, m), 4.17 (1H, d), 3.84 (2H, br d), 3.57 (1H, d), 3.30 (4H, br), 1.97-1.85 (5H, br m), 1.73 (1H, m), 0.95 (1H, dt), 0.74 (1H, q).

LCMS (Method C) r/t 3.33 (M+H) 473

Example 25

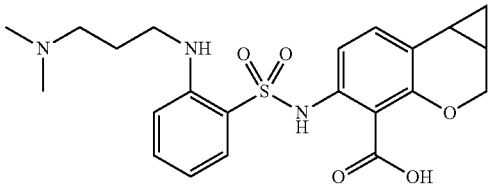
Second eluting enantiomer: r/t on analytical column 21.4 minutes, >98% ee

^{1}H NMR (DMSO-d_6) δ: 7.55 (1H, dd), 7.34 (1H, d), 7.24 (1H, dd), 7.19 (1H, dd), 7.14 (1H, d), 7.02 (1H, d), 6.14 (1H, dt), 4.17 (1H, d), 3.84 (2H, br d), 3.57 (1H, d), 3.29 (4H, br), 1.97-1.85 (5H, br m), 1.73 (1H, m), 0.95 (1H, dt), 0.74 (1H, q).

LCMS (Method C) r/t 3.34 (M+H) 473.

Example 26

(1aRS,7bSR)-5-[2-(3-Dimethylaminopropylamino) benzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclo-propa[c]chromene-4-carboxylic acid



A mixture of (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (Intermediate 67, 0.15 g), 3-dimethylaminopropylamine (1.26 g) and triethylamine (0.62 g) in NMP (6 mL) was stirred and heated at 140° C. for 48 hours. After cooling, the mixture was concentrated under vacuum and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 5-10%. The resultant product was repurified by preparative TLC, eluting with a mixture of methanol and DCM (10%) to give (1aRS,7bSR)-5-[2-(3-dimethylaminopropylamino)-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylic acid (0.08 g) as an off white solid.

^{1}H NMR (DMSO-d_6) δ: 7.36 (1H, dd), 7.22 (1H, dt),7.02 (2H, s), 6.68 (1H, d), 6.44 (1H, t), 6.24 (1H, br s), 4.11 (1H, d), 3.51 (1H, d), 3.30-3.10 (4H, m), 2.68 (6H, s), 1.83 (1H, m), 1.72-1.52 (3H, m), 0.85 (1H, m), 0.65 (1H, m).

LCMS (Method C) r/t 3.31 (M+H) 446.

Examples 27 and 28

Separation of Enantiomers from Example 26

Sample from Example 26 was subjected to chiral separation using a ChiralPak IB column 20 mm×250 mm, particle size 5 micron. Eluting solvent hexane:ethanol:diethylamine (49.8:50:0.2).

Example 27

First eluting enantiomer: r/t on analytical column (4.6 mm×250 mm) 14.61 minutes (>98% ee)

^{1}H NMR (DMSO-d_6) δ: 7.37 (1H, dd), 7.23 (1H, dt),7.02 (2H, s), 6.68 (1H, d), 6.45 (1H, t), 6.24 (1H, br s), 4.11 (1H, d), 3.52 (1H, d), 3.35-3.02 (4H, m), 2.67 (6H, s), 1.84 (1H, m), 1.74-1.52 (3H, m), 0.85 (1H, m), 0.66 (1H, m).

LCMS (Method C) r/t 3.21 (M+H) 446.

Example 28

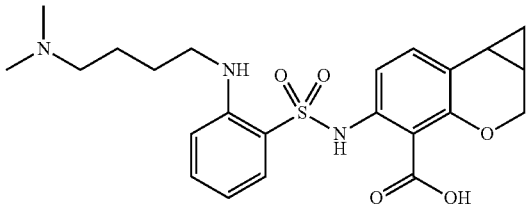
Second eluting enantiomer: r/t on analytical column (4.6 mm×250 mm) 18.16 minutes (>98% ee)

^{1}H NMR (DMSO-d_6) δ: 7.37 (1H, dd), 7.23 (1H, dt),7.02 (2H, s), 6.68 (1H, d), 6.44 (1H, t), 6.25 (1H, br s), 4.11 (1H, d), 3.51 (1H, d), 3.41-3.05 (4H, m), 2.69 (6H, s), 1.84 (1H, m), 1.74-1.52 (3H, m), 0.85 (1H, m), 0.66 (1H, m).

LCMS (Method C) r/t 3.20 (M+H) 446.

Example 29

(1aRS,7bSR)-5-[2-(4-Dimethylaminobutylamino) benzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclo-propa[c]chromene-4-carboxylic acid



Prepared by proceeding in a similar manner to Example 26, starting from (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (Intermediate 67) and 4-dimethylaminobutylamine.

^{1}H NMR (DMSO-d_6) δ: 13.0-12.0 (1H, br s), 7.58 (1H, dd), 7.28 (1H, dt), 7.02 (2H, s), 6.69 (1H, d), 6.55 (1H, t), 5.70 (1H, m),4.14 (1H, d), 3.53 (1H, d), 3.15 (2H, m), 2.91 (2H, m), 2.67 (6H, s), 1.83 (1H, m), 1.76 (2H, m), 1.66 (1H, m), 1.53 (2H, m), 0.84 (1H, m), 0.67 (1H, m).

LCMS (Method C) r/t 3.43 (M+H) 460.

Examples 30 and 31

Separation of Enantiomers from Example 29

Sample from Example 29 was subjected to chiral separation using a ChiralPak IB column 20 mm×250 mm, particle size 5 micron. Eluting solvent hexane:ethanol:diethylamine (49.8:50:0.2).

Example 30

First eluting enantiomer: r/t on analytical column (4.6 mm×250 mm) 12.69 minutes (>98% ee)

^{1}H NMR (DMSO-d_6) δ: 13.0-12.2 (1H, br s), 7.58 (1H, dd), 7.28 (1H, dt), 7.02 (2H, m), 6.69 (1H, d), 6.55 (1H, t), 5.71 (1H, m), 4.14 (1H, d), 3.53 (1H, d), 3.15 (2H, m), 2.89 (2H, m), 2.67 (6H, s), 1.83 (1H, m), 1.76 (2H, m), 1.66 (1H, m), 1.54 (2H, m), 0.85 (1H, m), 0.68 (1H, m).

LCMS (Method C) r/t 3.33 (M+H) 460.

Example 31

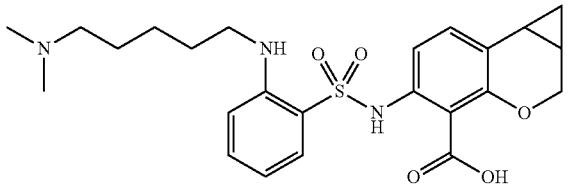
Second eluting enantiomer: r/t on analytical column (4.6 mm×250 mm) 16.82 minutes (>98% ee)

^{1}H NMR (DMSO-d_6) δ: 12.9-12.1 (1H, br s), 7.58 (1H, dd), 7.28 (1H, dt), 7.02 (2H, s), 6.70 (1H, d), 6.55 (1H, t), 5.71 (1H, m), 4.14 (1H, d), 3.53 (1H, d), 3.15 (2H, m), 2.91 (2H, m), 2.68 (6H, s), 1.83 (1H, m), 1.77 (2H, m), 1.66 (1H, m), 1.54 (2H, m), 0.85 (1H, m), 0.68 (1H, m).

LCMS (Method C) r/t 3.33 (M+H) 460.

Example 32

(1aRS,7bSR)-5-[2-(5-Dimethylaminopentylamino) benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



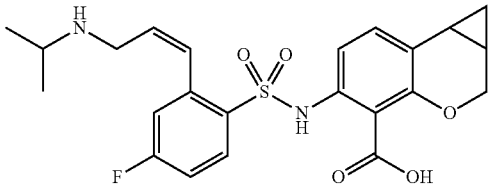
Prepared by proceeding in a similar manner to Example 26, starting from (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (Intermediate 67) and 5-dimethylaminopentylamine.

^{1}H NMR (DMSO-d_6) δ: 12.8-12.2 (1H, br s), 7.67 (1H, dd), 7.30 (1H, dt), 6.98 (1H, d), 6.85 (1H, d), 6.68 (1H, d), 6.60 (1H, t), 5.54 (1H, m), 4.14 (1H, d), 3.54 (1H, d), 3.05 (4H, m), 2.66 (6H, s), 1.81 (1H, m), 1.63 (5H, m), 1.51 (2H, m), 0.83 (1H, m), 0.67 (1H, m).

LCMS (Method C) r/t 3.55 (M+H) 474.

Example 33

(1aRS,7bSR)-5-{2[(Z)-3-(Propan-2-yl)aminoprop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



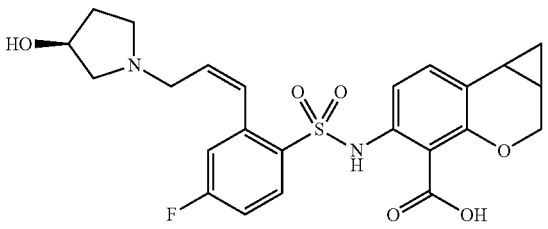
A mixture of methyl (1aRS,7bSR)-5-{2[(Z)-3-(propan-2-yl)aminoprop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 69, 0.12 g) and lithium hydroxide monohydrate (0.1 g) in a mixture of dioxane (10 mL) and water (5 mL) was stirred and heated at 100° C. overnight. After cooling, the mixture was concentrated under vacuum and the residue was acidified to pH4 with formic acid then extracted with a mixture of ethyl acetate and THF (1:1). The organic phase was dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was dissolved in ethyl acetate (2 mL) and hexane was added (10 mL). The solid was collected by filtration and washed with ether to give (1aRS,7bSR)-5-{2[(Z)-3-(propan-2-yl)aminoprop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylic acid (0.04 g) as an off white solid.

^{1}H NMR (DMSO-d_6) δ: 10.5-9.8 (1H, br s), 7.54 (1H, dd), 7.23-7.08 (3H, m), 7.04 (1H, d), 6.96 (1H, d), 5.91 (1H, m), 4.09 (1H, d), 3.63 (2H, m), 3.53 (1H, m), 3.49 (1H, d), 1.85 (1H, m), 1.67 (1H, m), 1.16 (6H, d), 0.86 (1H, m), 0.67 (1H, m).

LCMS (Method C) r/t 3.37 (M+H) 461.

Example 34

(1aRS,7bSR)-5-{2[(Z)-3-((S)-3-Hydroxypyrrolidin-1-yl)aminoprop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylic acid



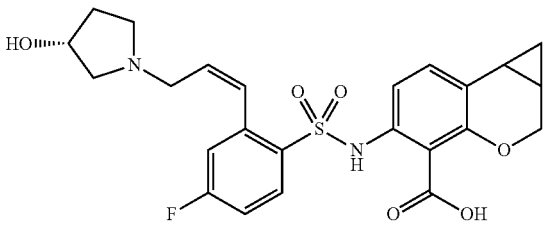
Prepared by proceeding in a similar manner to Example 33, starting from methyl (1aRS,7bSR)-5-{2[(Z)-3-((S)-3-hydroxypyrrolidin-1-yl)aminoprop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylate (Intermediate 70).

^{1}H NMR (DMSO-d_6) δ: 12.5-11.3 (1H, br s), 7.62 (1H, m), 7.32 (1H, d), 7.22 (2H, m), 7.13 (1H, d), 6.98 (1H, d), 6.12 (1H, m), 5.26 (1H, m), 4.37 (1H, m), 4.19 (1H, d), 3.79 (2H, m), 3.59 (1H, dd), 3.20-3.00 (3H, br s), 2.05 (1H, m), 1.94 (1H, m), 1.77 (2H, m), 0.96 (1H, m), 0.76 (1H, m).

LCMS (Method C) r/t 3.15 (M+H) 489.

Example 35

(1aRS,7bSR)-5-{2[(Z)-3-((R)-3-Hydroxypyrrolidin-1-yl)aminoprop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c] chromene-4-carboxylic acid



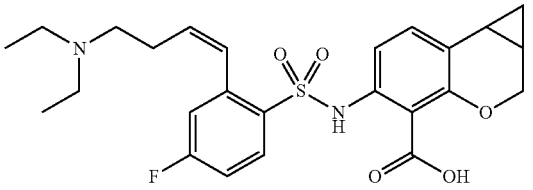
Prepared by proceeding in a similar manner to Example 33, starting from methyl (1aRS,7bSR)-5-{2[(Z)-3-((R)-3-hydroxypyrrolidin-1-yl)aminoprop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylate (Intermediate 71).

^{1}H NMR (DMSO-d_6) δ: 12.5-11.4 (1H, br s), 7.62 (1H, m), 7.33 (1H, d), 7.22 (2H, m), 7.13 (1H, d), 6.98 (1H, d), 6.14 (1H, m), 5.26 (1H, m), 4.37 (1H, m), 4.19 (1H, d), 3.79 (2H, m), 3.59 (1H, dd), 3.20-3.00 (3H, br s), 2.05 (1H, m), 1.94 (1H, m), 1.77 (2H, m), 0.96 (1H, m), 0.76 (1H, m).

LCMS (Method C) r/t 3.14 (M+H) 489.

Example 36

(1aRS,7bSR)-5-[2((Z)-4-Diethylaminobut-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid



Prepared by proceeding in a manner similar to Example 33, starting from methyl (1aRS,7bSR)-5-{N-(methoxycarbonyl)-N-[2((Z)-4-diethylaminobut-1-enyl)-4-fluorobenzenesulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 72).

^{1}H NMR (DMSO-d_6) δ: 12.8-11.4 (1H, br s), 7.54 (1H, dd), 7.14-7.02 (4H, m), 6.83 (1H, d), 5.66 (1H, m), 4.09 (1H, d), 3.51 (1H, d), 3.13 (2H, m), 2.92 (4H, m), 2.34 (2H, m), 1.84 (1H, m), 1.66 (1H, m), 1.06 (6H, t), 0.86 (1H, m), 0.67 (1H, m).

LCMS (Method C) r/t 3.35 (M+H) 489.

Examples 37 and 38

Separation of Enantiomers from Example 36

Sample from Example 37 was subjected to chiral separation using a ChiralPak IC column, 10 mm×250 mm, particle size 5 micron. Eluting solvent tert-butyl methyl ether:isopropanol:DCM (16:20:64).

Example 37

First eluting enantiomer: r/t on analytical column (4.6 mm×250 mm): 25.8 minutes>98% ee

^{1}H NMR (DMSO-d_6) δ: 7.61 (1H, dd), 7.20-7.09 (4H, m), 6.90 (1H, d), 5.74 (1H, m), 4.16 (1H, d), 3.58 (1H, d), 3.22-3.11 (2H, m), 2.99 (4H, m), 2.50 (2H, m), 1.92 (1H, dt), 1.72 (1H, m), 1.15 (6H, t), 0.93 (1H, m), 0.75 (1H, m).

LCMS (Method C) r/t 3.36 (M+H) 489

Example 38

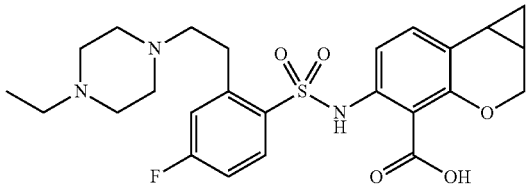
Second eluting enantiomer: r/t on analytical column 44.0 minutes, >98% ee

^{1}H NMR (DMSO-d_6) δ: 7.61 (1H, dd), 7.20-7.10 (4H, m), 6.90 (1H, d), 5.74 (1H, m), 4.16 (1H, d), 3.58 (1H, d), 3.23-3.10 (2H, m), 2.99 (4H, q), 2.51 (2H, m), 1.92 (1H, dt), 1.72 (1H, m), 1.15 (6H, t), 0.93 (1H, m), 0.75 (1H, m).

LCMS (Method C) r/t 3.36 (M+H) 489

Example 39

(1aRS,7bSR)-5-{2-[2-(4-Ethylpiperazin-1-yl)-ethyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



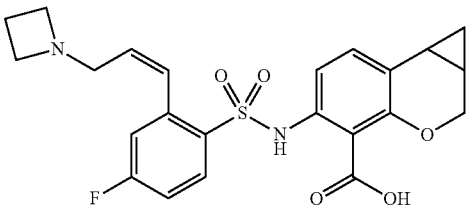
A solution of (1aRS,7bSR)-5-(4-Fluoro-2-vinylbenzenesulfonylamino)-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid (Intermediate 74, 0.035 g) and 3 drops of N-ethyl piperazine in isopropanol (0.5 mL) was irradiated in the microwave at 160° C. for 15 minutes then again at 170° C. for 15 minutes. After cooling, the mixture was purified by preparative HPLC (C18) eluting with a mixture of methanol and water, containing 0.1% formic acid, with a gradient of 20-60%. The isolated product was further purified by chromatography on silica eluting with a mixture of methanol and DCM with a gradient of 0-10% to give (1aS,7bR)-5-{2-[2-(4-ethylpiperazin-1-yl)-ethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.018 g) as an off white solid.

^{1}H NMR ($CDCl_3$) δ: 7.95 (1H, dd), 7.07 (2H, s), 6.95 (1H, dd), 6.91 (1H, dt), 4.38 (1H, d), 3.79 (1H, d), 3.42 (2H, q), 3.35 (2H, q), 3.21-3.05 (4H, m), 3.04-2.88 (4H, m), 2.79 (2H, m), 1.86 (1H, dt), 1.66 (1H, m), 1.22 (3H, t), 1.06 (1H, q), 0.93 (1H, m).

LCMS (Method C) r/t 2.95 (M+H) 504

Example 40

(1aRS,7bSR)-5-{2[(Z)-3-(Azetidin-1-yl)prop-1-enyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



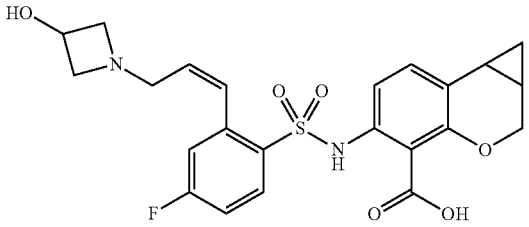
Prepared by proceeding in a manner similar to Example 33, staring from methyl (1aRS,7bSR)-5-{2[(Z)-3-(azetidin-1-yl) prop-1-enyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (Intermediate 76).

^{1}H NMR (DMSO-d_6) δ: 12.8-11.1 (1H, br s), 7.51 (1H, dd), 7.26 (1H, d), 7.17 (1H, dt), 7.10 (2H, m), 7.00 (1H, d), 5.90 (1H, m), 4.12 (1H, d), 3.96 (4H, m), 3.74 (2H, m), 3.52 (1H, d), 2.27 (2H, m), 1.89 (1H, m), 1.69 (1H, m), 0.90 (1H, m), 0.69 (1H, m).

LCMS (Method C) r/t 3.26 (M+H) 459.

Example 41

(1aRS,7bSR)-5-{2[(Z)-3-(3-Hydroxyazetidin-1-yl) prop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a, 2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



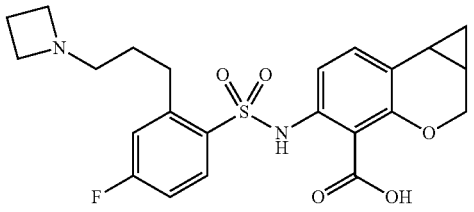
Prepared by proceeding in a manner similar to Example 33, starting from methyl (1aRS,7bSR)-5-{2[(Z)-3-(3-hydroxyazetidin-1-yl)prop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 77).

^{1}H NMR (DMSO-d_6) δ: 12.8-11.2 (1H, br s), 7.53 (1H, m), 7.22 (1H, d), 7.17 (1H, dt), 7.09 (2H, m), 6.97 (1H, d), 5.90 (1H, m), 4.40 (1H, m), 4.18 (2H, m), 4.12 (1H, d), 3.69 (4H, m), 3.52 (1H, d), 1.87 (1H, m), 1.69 (1H, m), 0.89 (1H, m), 0.70 (1H, m).

LCMS (Method C) r/t 3.18 (M+H) 475.

Example 42

(1aRS,7bSR)-5-{2[(Z)-3-(Azetidin-1-yl)propyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



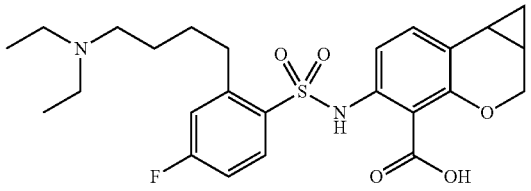
A solution of (1aRS,7bSR)-5-{2[(Z)-3-(azetidin-1-yl) prop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (Example 40, 0.03 g) in methanol was treated, under an atmosphere of nitrogen with palladium on carbon (10%, 0.01 g). The nitrogen was replaced by hydrogen and the mixture was stirred under an atmosphere of hydrogen overnight. The mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by HPLC (C18) to give (1aRS, 7bSR)-5-{2[(Z)-3-(azetidin-1-yl)propyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylic acid (0.019 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.76 (1H, dd), 7.20 (1H, dd), 7.09 (1H, dt), 7.05 (1H, d), 6.99 (1H, d) 4.15 (1H, d), 3.97 (2H, m) 3.56 (1H, d), 3.14 (2H, m), 2.99 (4H, m), 2.29 (2H, m), 1.86 (1H, m), 1.81-1.64 (3H, m), 0.88 (1H, m), 0.69 (1H, m).

^{1}H LCMS (Method C) r/t 3.20 (M+H) 461.

Example 43

(1aRS,7bSR)-5-[2((Z)-4-Diethylaminobutyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



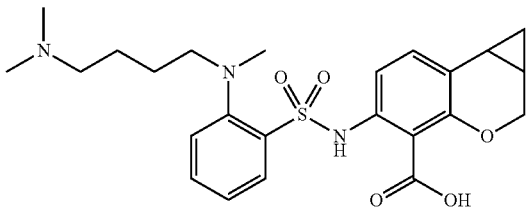
Prepared by proceeding in a similar manner to Example 42, starting from (1aRS,7bSR)-5-[2((Z)-4-diethylaminobut-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (Example 36) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 13.0-11.6 (1H, br s), 7.82 (1H, dd), 7.21 (1H, dd), 7.08 (1H, dt), 7.02 (1H, d), 6.96 (1H, d), 4.14 (1H, d), 3.55 (1H, d), 2.99 (8H, m), 1.83 (1H, m), 1.65 (5H, m), 1.14 (6H, t), 0.85 (1H, m), 0.69 (1H, m).

LCMS (Method C) r/t 3.45 (M+H) 491.

Example 44

(1aRS,7bSR)-5-{2-[N-(4-Dimethylaminobutyl)-N-methylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



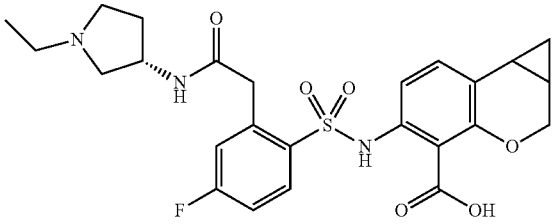
A mixture of (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (Intermediate 67, 0.1 g), N-(4-dimethylaminobutyl)-N-methylamine (Intermediate 78, 1.07 g) and triethylamine (0.42 g) in NMP (6 mL) was stirred and heated in a sealed tube at 150° C. for 3 days. After cooling, the mixture was concentrated under vacuum and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM (10%) followed by repurification by HPLC (C18) to give (1aRS,7bSR)-5-{2-[N-(4-dimethylaminobutyl)-N-methylamino]-benzenesulfonylamino}-1,1a,2, 7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.03 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.81 (1H, dd), 7.54 (1H, dt), 7.41 (1H, dd), 7.21 (1H, dt), 6.94 (1H, d), 6.85 (1H, d), 4.12 (1H, d), 3.55 (1H, d), 2.96 (2H, t), 2.85 (2H, t), 2.64 (6H, s), 2.49 (3H, s), 1.83 (1H, m), 1.74 (2H, m), 1.63 (3H, m), 0.87 (1H, m), 0.68 (1H, m).

LCMS (Method C) r/t 3.37 (M+H) 474.

Example 45

(1aRS,7bSR)-5-{2-[((S)-1-Ethylpyrrolidin-3-ylcarbamoyl)methyl]-4-fluoro-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



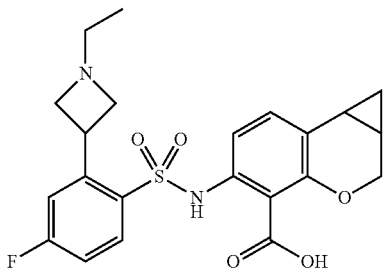
A mixture of methyl (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-3-ylcarbamoyl)methyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 80, 0.148 g) and lithium hydroxide monohydrate (0.168 g) in dioxane (3 mL) and water (1 mL) was irradiated in the microwave at 130° C. for 40 minutes. After cooling, the mixture was diluted with methanol, acidified with formic acid and evaporated in vacuo. The residue was triturated with 10% methanol in DCM and filtered. The filtrate was evaporated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-20%. The resultant solid was triturated with ether and filtered off to give (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-3-ylcarbamoyl)methyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.091 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 9.56 (0.5H, br, d), 9.48 (0.5H, br, d), 7.59 (1H, m), 7.34 (1H, m), 7.16 (2H, m), 7.06 (1H, t), 4.46 (1H, br, q), 4.13 (1H, d), 3.92 (1H, dd), 3.70 (1H, m), 3.65 (1H, d), 3.58 (1H, br, m), 2.95-3.25 (6H, m), 2.40 (1H, m), 1.95 (2H, m), 1.76 (1H, m), 1.20 (3H, t), 0.97 (1H, m), 0.78 (1H, m).

LCMS (Method C) r/t 3.04 (M+H) 518.

Example 46

(1aRS,7bSR)-5-[2-(1-Ethylazetidin-3-yl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



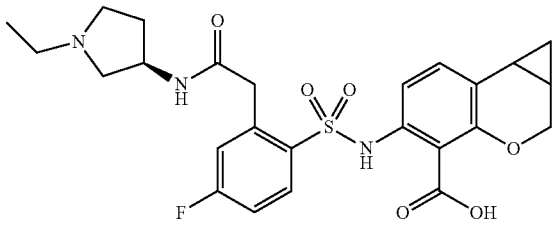
Prepared by proceeding in a similar manner to Example 45, starting from methyl (1aRS,7bSR)-5-[2-(1-ethylazetidin-3-yl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 86) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.91 (1H, dd), 7.64 (1H, dd), 7.24 (1H, dt), 6.96 (1H, d), 6.66 (1H, d), 4.79 (1H, m), 4.21 (1H, d), 4.15 (2H, br, t), 3.89 (2H, br, m), 3.62 (1H, d), 3.06 (2H, q), 1.83 (1H, m), 1.70 (1H, m), 1.05 (3H, t), 0.88 (1H, m), 0.72 (1H, m).

LCMS (Method C) r/t 2.99 (M+H) 447.

Example 47

(1aRS,7bSR)-5-{2-[((R)-1-Ethylpyrrolidin-3-ylcarbamoyl)methyl]-4-fluoro-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



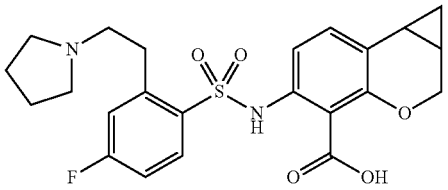
Prepared by proceeding in a similar manner to Example 45, starting from methyl (1aRS,7bSR)-5-{2-[((R)-1-ethylpyrrolidin-3-ylcarbamoyl)methyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 92) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 10.30 (0.5H, br, s), 10.25 (0.5H, br, s), 9.88 (1H, br, s), 7.52 (1H, m), 7.18-7.41 (3H, m), 6.75 (1H, m), 4.83 (0.5H, m), 4.70 (0.5H, m), 4.17 (1.5H, m), 3.84-4.10 (1.5H, m), 3.60-3.86 (3H, m), 3.45 (0.5H, d), 3.31 (0.5H, m), 3.13 (0.5H, m), 2.98 (0.5H, m), 2.83 (2H, m), 2.46 (1H, m), 2.29 (1H, m), 1.93 (1H, m), 1.67 (1H, q), 1.40 (3H, t), 1.13 (0.5H, m), 1.07 (0.5H, m), 0.97 (1H, m).

LCMS (Method C) r/t 3.03 (M+H) 518.

Example 48

(1aRS,7bSR)-5-{2-[2-(Pyrrolidin-1-yl)-ethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



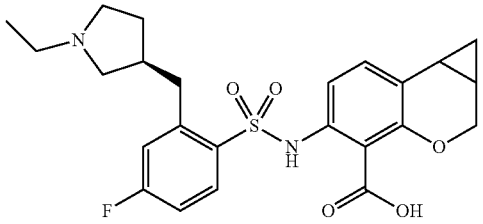
Prepared by proceeding in a similar manner to Example 39, starting from (1aRS,7bSR)-5-(4-fluoro-2-vinylbenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (Intermediate 74) and pyrrolidine as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.84 (1H, dd), 7.26 (1H, dd), 7.17 (1H, dt), 7.02 (1H, d), 6.74 (1H, d), 4.16 (1H, d), 3.59 (1H, d), 3.36-3.20 (8H, m), 1.91 (4H, m), 1.85 (1H, m), 1.69 (1H, m), 0.89 (1H, m), 0.70 (1H, m).

LCMS (Method C) r/t 3.12 (M+H) 461.

Example 49

(1aRS,7bSR)-5-[2-((R)-1-Ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



Lithium hydroxide (0.111 g) was added to a solution of methyl (1aRS,7bSR)-5-[2-((R)-1-ethyl-pyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 95, 0.13 g) in a mixture of dioxane (4 mL) and water (1 mL) and the mixture was stirred and heated at 85° C. overnight. After cooling, the mixture was filtered and the filtrate was acidified by addition of 10% aqueous citric acid (1 mL) and then extracted with DCM. The organic extract was dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was triturated with diethyl ether and the solid was collected by filtration to give (1aRS,7bSR)-5-[2-((R)-1-ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.085 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.81 (1H, dd), 7.28 (1H, dd), 7.16 (1H, dt), 7.11 (1H, dd), 6.99 (1H, dd), 4.20 (1H, dd), 3.60 (1H, t), 3.48-2.98 (9H, br m), 2.25 (1H, m), 1.91 (1H, dt), 1.73 (2H, m), 1.23 (3H, t), 0.93 (1H, dt), 0.75 (1H, m).

LCMS (Method C) r/t 3.21 (M+H) 475.

Examples 50 and 51

Separation of Enantiomers from Example 49

Sample from Example 49 was subjected to chiral separation using a ChiralPak IC column, 10 mm×250 mm, particle size 5 micron. Eluting solvent tert-butyl methyl ether:isopropanol:DCM (10:15:75).

Example 50

First eluting enantiomer: r/t on analytical column (4.6 mm×250 mm): 30.0 minutes>99% ee

^{1}H NMR (DMSO-d_6) δ: 7.81 (1H, dd), 7.27 (1H, dd), 7.15 (1H, dt), 7.10 (1H, d), 7.01 (1H, d), 4.20 (1H, d), 3.58 (1H, d), 3.23-3.11 (6H, m), 3.11-3.06 (3H, m), 2.25 (1H, m), 1.91 (1H, dt), 1.73 (2H, m), 1.22 (3H, t), 0.92 (1H, dt), 0.73 (1H, m).

LCMS (Method C) r/t 3.25 (M+H) 475.

Example 51

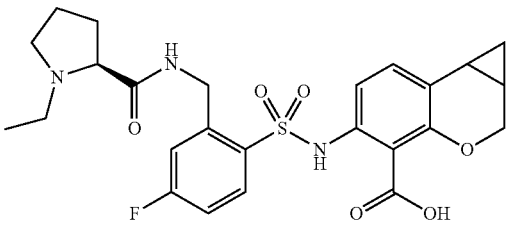
Second eluting enantiomer: r/t on analytical column 40.0 minutes, >99% ee

^{1}H NMR (DMSO-d_6) δ: 7.80 (1H, dd), 7.27 (1H, dd), 7.15 (1H, dt), 7.10 (1H, d), 7.03 (1H, d), 4.18 (1H, d), 3.61 (1H, d), 3.48-2.97 (9H, br m), 2.27 (1H, m), 1.91 (1H, dt), 1.71 (2H, m), 1.23 (3H, t), 0.93 (1H, dt), 0.74 (1H, m).

LCMS (Method C) r/t 3.23 (M+H) 475.

Example 52

(1aRS,7bSR)-5-{2-[((S)-1-Ethylpyrrolidin-2-yl)cabonylaminomethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



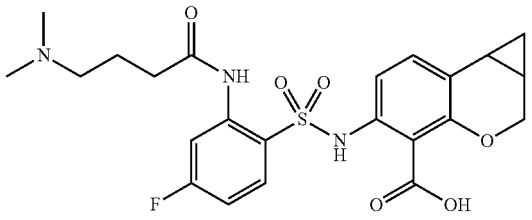
A mixture of methyl (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-2-yl)cabonylaminomethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 101, 0.212 g) and lithium hydroxide (0.05 g) in dioxane (5.5 mL) and water (2.5 mL) was irradiated in the microwave at 150° C. for 30 minutes. After cooling, the mixture was diluted with water, acidified with formic acid to pH5 and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporate to dryness and the residue was purified by HPLC (C18) eluting with a mixture of methanol and water, containing 0.1% formic acid, with a gradient of 35-75% to give (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-2-yl)cabonylaminomethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (0.064 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 10.8-9.6 (1H, br s), 8.90 (1H, br t), 7.71 (1H, m), 7.20 (3H, m), 6.86 (1H, m), 4.88 (2H, m), 4.37 (1H, dd), 3.85 (1H, dt), 3.61 (1H, m), 3.43 (1H, m), 2.97 (1H, m), 2.77 (2H, m), 2.23 (2H, m), 2.03 (1H, m), 1.91 (2H, m), 1.69 (1H, m), 1.18 (3H, q), 1.01 (2H, m).

LCMS (Method C) r/t 3.09 (M+H) 518.

Example 53

(1aRS,7bSR)-5-[2-(4-Dimethylaminobutyrylamino)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



A mixture of methyl (1aRS,7bSR)-5-[2-(4-dimethylaminobutyryl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 108, 0.2 g), potassium carbonate (0.22 g), 1H-pyrazole-3-

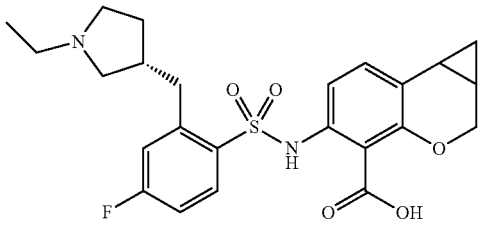
amine (0.34 g) and lithium iodide (1.07 g) in DMF (10 mL) was irradiated in the microwave at 150° C. for 1 hour. After cooling, the mixture was diluted with methanol and acidified to pH 3 with formic acid then concentrated under vacuum. The residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM (5%). The resultant product was purified by HPLC (C18) to give (1aRS,7bSR)-5-[2-(3-dimethylaminobutyryl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (0.03 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.95 (1H, dd), 7.80 (1H, dd), 6.96 (1H, d), 6.95 (1H, dt), 6.79 (1H, d), 4.13 (1H, d), 3.56 (1H, d), 3.04 (2H, t), 2.68 (6H, s), 2.56 (2H, t), 1.94 (2H, m), 1.81 (1H, m), 1.64 (1H, m), 0.84 (1H, m), 0.66 (1H, m).

LCMS (Method C) r/t 3.12 (M+H) 492.

Example 54

(1aRS,7bSR)-5-[2-((S)-1-Ethylpyrrolidin-3-ylm-ethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



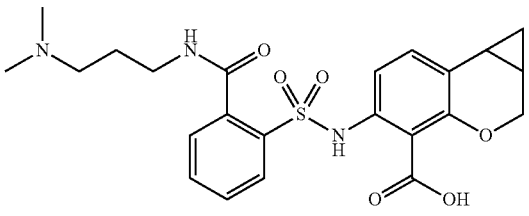
Prepared by proceeding in a similar manner to Example 49, starting from methyl (1aRS,7bSR)-5-[2-((S)-1-ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (Intermediate 113).

^{1}H NMR (DMSO-d_6) δ: 7.81 (1H, dd), 7.27 (1H, dd), 7.15 (1H, dt), 7.10 (1H, d), 7.02 (1H, dd), 4.19 (1H, dd), 3.56 (1H, t), 3.23-3.11 (6H, m), 3.11-3.06 (3H, m), 2.25 (1H, m), 1.91 (1H, dt), 173 (2H, m), 1.22 (3H, t), 0.92 (1H, dt), 0.73 (1H, m).

LCMS (Method C) r/t 3.21 (M+H) 475.

Example 55

(1aRS,7bSR)-5-[2-(3-Dimethylaminopropylcarbam-oyl)benzenesulfonylamino]-1,1a,2,7b-tetrahydrocy-clopropa-[c]chromene-4-carboxylic acid



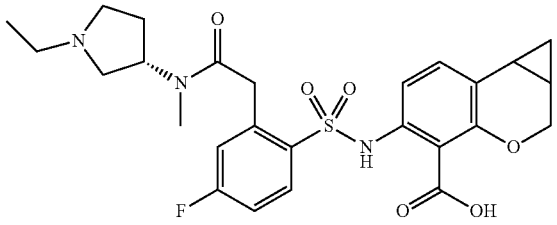
A solution of tert-butyl (1aRS,7bSR)-5-{2-[N-(2,4-dimethoxybenzyl)-N-(3-dimethylamino-propyl)carbamoyl] benzenesulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa-[c]chromene-4-carboxylate (Intermediate 119, 0.03 g) in trifluoroacetic acid (5 mL) was stirred and heated at 30° C. overnight. The mixture was evaporated to dryness and the residue was purified by HPLC (C18) to give (1aRS,7bSR)-5-[2-(3-dimethylaminopropylcarbamoyl)benzenesulfony-lamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.013 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 8.61 (1H, br t), 7.73 (1H, d), 7.52 (1H, t), 7.43 (2H, m), 6.97 (1H, d), 6.82 (1H, d), 4.14 (1H, d), 3.58 (1H, d), 3.26 (2H, m), 3.04 (2H, t), 2.60 (6H, s), 1.85 (3H, m), 1.67 (1H, m), 0.87 (1H, m), 0.68 (1H, m).

LCMS (Method C) r/t 2.79 (M+H) 473.

Example 56

(1aRS,7bSR)-5-(2-{[N—((S)-1-Ethylpyrrolidin-3-yl)-N-methylcarbamoyl]methyl}-4-fluorobenzene-sulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylic acid



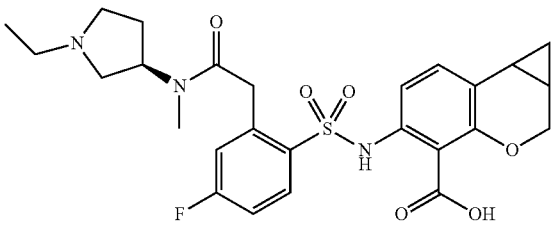
A mixture of methyl (1aRS,7bSR)-5-(2-{[N—((S)-1-ethylpyrrolidin-3-yl)-N-methylcarbamoyl]-methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa [c]chromene-4-carboxylate (Intermediate 126, 0.047 g) and lithium hydroxide monohydrate (0.168 g) in dioxane (3 mL) and water (1 mL) was irradiated in the microwave at 130° C. for 40 minutes. After cooling, the mixture was diluted with methanol, acidified with formic acid and evaporated in vacuo. The residue was triturated with 10% methanol in DCM, filtered and the filtrate was evaporated in vacuo. The residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-40%. The resultant solid was triturated with ethyl acetate and filtered off to give (1aRS,7bSR)-5-(2-{[N—((S)-1-ethylpyrrolidin-3-yl)-N-methylcarbamoyl]-methyl}-4-fluorobenzenesulfony-lamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.022 g) as a white solid.

^{1}H NMR (DMSO-d_6 at 80° C.) δ: 7.83 (1H, t), 7.12 (1H, dt), 7.08 (1H, d), 7.01 (1H, d), 6.84 (1H, m), 4.61 (1H, br, s), 4.19 (1H, d), 4.12 (2H, s), 3.73 (1H, d), 2.71-3.18 (7H, br, m), 2.94 (3H, s), 1.85-2.15 (3H, m), 1.72 (1H, m), 1.17 (3H, t), 0.95 (1H, m), 0.78 (1H, m).

LCMS (Method C) r/t 3.08 (M+H) 532.

Example 57

(1aRS,7bSR)-5-(2-{[N—((R)-1-Ethylpyrrolidin-3-yl)-N-methylcarbamoyl]methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



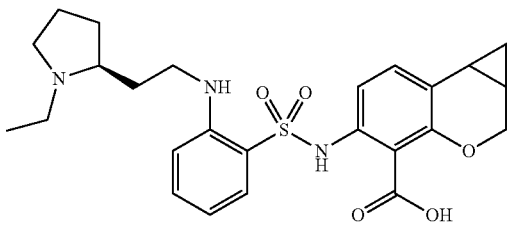
A mixture of methyl (1aRS,7bSR)-5-(2-{[N—((R)-1-ethylpyrrolidin-3-yl)methylcarbamoyl]-N-methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 131, 0.076 g) and lithium hydroxide monohydrate (0.168 g) in dioxane (3 mL) and water (1 mL) was irradiated in the microwave at 130° C. for 40 minutes. After cooling the mixture was diluted with methanol, acidified with formic acid and evaporated in vacuo. The residue was triturated with 10% methanol in DCM, filtered and the filtrate was evaporated in vacuo. The residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-40%. The resultant solid was triturated with ethyl acetate and filtered off to give (1aRS,7bSR)-5-(2-{[N—((R)-1-ethylpyrrolidin-3-yl)-N-methylcarbamoyl]-methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.028 g) as a white solid.

^{1}H NMR (DMSO-d_6 at 80° C.) δ: 7.83 (1H, t), 7.12 (1H, dt), 7.08 (1H, d), 7.01 (1H, d), 6.84 (1H, m), 4.61 (1H, br, s), 4.19 (1H, d), 4.12 (2H, s), 3.73 (1H, d), 2.71-3.18 (7H, br, m), 2.94 (3H, s), 1.85-2.15 (3H, m), 1.72 (1H, m), 1.17 (3H, t), 0.95 (1H, m), 0.78 (1H, m).

LCMS (Method C) r/t 3.08 (M+H) 532.

Example 58

(1aRS,7bSR)-5-{2-[2-((S)-1-Ethylpyrrolidin-2-yl)ethylamino]benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



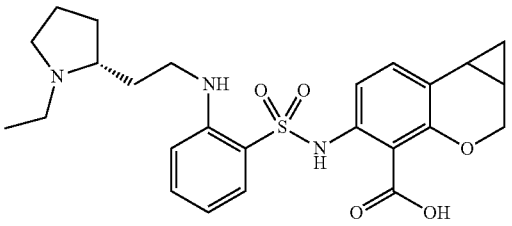
A mixture of (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (Intermediate 67, 0.1 g), 2-((S)-1-ethylpyrrolidin-2-yl)ethylamine (Intermediate 136, 0.5 g) and triethylamine (0.5 mL) was stirred and heated in a sealed tube at 140° C. overnight. After cooling, the mixture was concentrated under vacuum and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM (10%). The product was repurified by HPLC (C18) to give (1aRS,7bSR)-5-{2-[2-((S)-1-ethylpyrrolidin-2-yl)ethylamino]benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.022 g) as a white solid.

NMR (DMSO-d_6) δ: 7.47 (1H, m), 7.25 (1H, t), 6.92 (1H, d), 6.89 (1H, m), 6.72 (1H, d), 6.53 (1H, dt),6.0-5.3 (1H, br s), 4.11 (1H, dd), 3.53 (1H, t), 3.33-2.80 (7H, m), 2.19 (2H, m), 1.92 (2H, m), 1.82 (2H, m), 1.64 (2H, m), 1.17 (3H, t), 0.84 (1H, m), 0.67 (1H, m).

LCMS (Method C) r/t 3.34 (M+H) 486.

Example 59

(1aRS,7bSR)-5-{2-[2-((R)-1-Ethylpyrrolidin-2-yl)ethylamino]benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



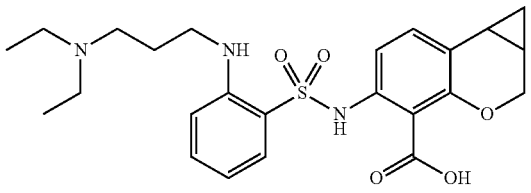
Prepared by proceeding in a similar manner to Example 58, starting from (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (Intermediate 67) and 2-((R)-1-ethylpyrrolidin-2-yl)ethylamine (Intermediate 141).

^{1}H NMR (DMSO-d_6) δ: 7.47 (1H, m), 7.25 (1H, t), 6.97 (1H, d), 6.90 (1H, m), 6.72 (1H, d), 6.53 (1H, dt), 6.0-5.4 (1H, br s), 4.12 (1H, dd), 3.53 (1H, t), 3.35-2.85 (7H, m), 2.20 (2H, m), 1.93 (2H, m), 1.81 (2H, m), 1.65 (2H, m), 1.18 (3H, t), 0.84 (1H, m), 0.67 (1H, m).

LCMS (Method C) r/t 3.32 (M+H) 486.

Example 60

(1aRS,7bSR)-5-[2-(3-N,N,-Diethylaminopropylamino)benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



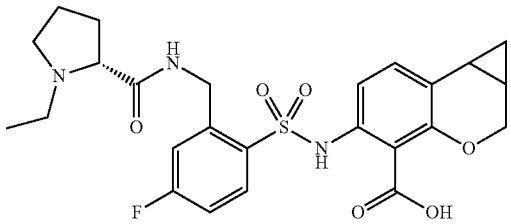
3-Diethylaminopropyl amine (0.975 g) was added to a solution of (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (Intermediate 67, 0.091 g) in NMP (3 mL) and the mixture was heated at 140° C. in a sealed tube for 36 hours. After cooling, the mixture was diluted with water (2 mL) and the solution was purified by preparative HPLC (C18) eluting with a mixture of methanol and water, containing 0.1% formic acid, with a gradient of 10-98% to give (1aRS,7bSR)-5-[2-(3-diethylaminopropylamino)benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.039 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.45 (1H, dd), 7.28 (1H, dt), 7.04 (2H, m), 6.74 (1H, d), 6.51 (1H, t), 6.17 (1H, br s), 4.16 (1H, d), 3.57 (1H, d), 3.54-2.97 (8H, br m), 1.87 (1H, dt), 1.81-1.63 (3H, m), 1.15 (6H, t), 0.89 (1H, m), 0.72 (1H, m).

LCMS (Method C) r/t 3.31 (M+H) 474.

Example 61

(1aRS,7bSR)-5-(2-{[((R)-1-Ethylpyrrolidine-2-yl) carbonylamino]methyl}-4-fluorobenzenesulfony-lamino)-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylic acid



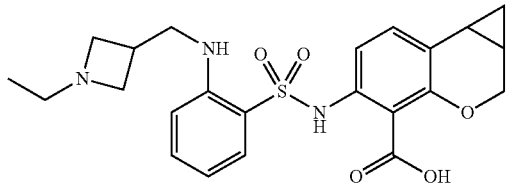
A mixture of methyl (1aRS,7bSR)-5-(2-{[((R)-1-ethylpyrrolidine-2-yl)carbonylamino]methyl}-4-fluorobenzene-sulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylate (Intermediate 146, 0.120 g) and lithium hydroxide monohydrate (0.095 g) was suspended in dioxane (5 mL) and water (1 mL) and the mixture was stirred and heated at 110° C. for 22.5 hours. After cooling, the volatiles were removed in vacuo and the residue was acidified by addition of aqueous citric acid solution (10%) and extracted with DCM. The organic layer was dried (Na_2SO_4) and filtered and the filtrate was evaporated to dryness. The residue was purified by preparative HPLC (C18) eluting with a mixture of methanol and water, containing 0.1% formic acid, with a gradient of 10-98% to give (1aRS,7bSR)-5-(2-{[((R)-1-ethylpyrrolidine-2-yl)carbonylamino]methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclo-propa-[c]chromene-4-carboxylic acid (0.043 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 8.77 (1H, d), 7.83 (1H, dd), 7.22 (1H, td), 7.12 (1H, dd), 7.08 (1H, d), 6.16 (1H, dd), 4.73 (2H, d), 4.24 (1H, d), 3.67 (1H, d), 3.54 (1H, br s), 3.37-3.28 (1H, m), 2.93-2.80 (1H, m), 2.80-2.61 (2H, m), 2.30-2.20 (1H, m), 1.95-1.70 (5H, m), 1.08 (3H, t), 0.95 (1H, dt), 0.76 (1H, q).

LCMS (Method C) r/t 3.09 (M+H) 518.

Example 62

(1aRS,7bSR)-5-{2-[(1-Ethylazetidin-3-ylmethyl) amino]benzene-sulfonylamino}-1,1a,2,7b-tetrahy-drocyclopropa[c]chromene-4-carboxylic acid



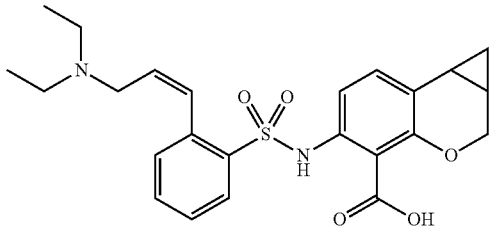
A mixture of (1aRS,7bSR)-5-(2-fluorobenzenesulfony-lamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic (Intermediate 67, 0.07 g) and (1-ethylazetidin-3-yl)methylamine (Intermediate 149, 0.7 g) in DMSO (1.4 mL) was divided evenly between 7 microwave vials and each was irradiated in the microwave at 130° C. for 4 hours. After cooling, the combined mixture was concentrated under vacuum and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM (10%). The product was repurified by HPLC (C18) to give (1aRS, 7bSR)-5-{2-[(1-ethylazetidin-3-ylmethyl)amino]benzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylic acid (0.012 g) as an off-white solid.

^{1}H NMR (DMSO-d_6) δ: 7.34 (1H, d), 7.22 (1H, t), 7.04 (1H, d), 6.97 (1H, d), 6.74 (1H, d), 6.49 (1H, t), 6.34 (1H, br s), 4.10 (1H, d), 3.75-3.55 (4H, m), 3.18 (1H, br m), 3.03 (1H, br m), 2.88 (2H, m), 2.32 (1H, m), 1.85 (1H, m), 1.67 (1H, m), 1.19 (1H, m), 0.98 (3H, t), 0.86 (1H, m), 0.69 (1H, m)

LCMS (Method C) r/t 3.21 (M+H) 457.

Examples 63 and 64

(1aR,7bS)-5-[2-((Z)-3-Diethylaminoprop-1-enyl) benzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclo-propa[c]chromene-4-carboxylic acid and (1aS,7bR)-5-[2-((Z)-3-diethylaminoprop-1-enyl) benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid



A mixture of methyl (1aRS,7bSR)-5-[2-((Z)-3-diethy-laminoprop-1-enyl)benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 153, 0.495 g) and lithium hydroxide monohydrate (0.442 g) was suspended in dioxane (20 mL) and water (5 mL) and the mixture was stirred and heated at 80° C. for 12.5 hours. After cooling, the volatiles were removed in vacuo and the residue was acidified by addition of aqueous citric acid solution (10%) and extracted with DCM. The organic layer was dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by preparative HPLC (C18) eluting with a mixture of acetonitrile and water, containing 0.1% formic acid, with a gradient of 35-70% to give (1aRS, 7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)benzenesulfo-nylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.147 g) as a white solid.

This material was subjected to chiral separation using a ChiralPak IC column, 4.6 mm×250 mm, particle size 5 micron. Eluting solvent absolute ethanol,

Example 63

First eluting enantiomer: retention time on above column: 25.71 minutes, >99% ee

^{1}H NMR (DMSO-d_6) δ: 7.65 (1H, dd), 7.60 (1H, td), 7.44-7.37 (2H, m), 7.28 (1H, d), 7.08 (1H, d), 6.95 (1H, d),

6.15-6.05 (1H, m), 4.16 (1H, d), 3.77-3.67 (2H, m), 3.56 (1H, d), 3.13-3.03 (4H, m), 1.90 (1H, dt), 1.71 (1H, q), 1.12 (6H, t), 0.92 (1H, dt), 0.72 (1H, q).

LCMS (Method C) r/t 3.20 (M+H) 457.

Example 64

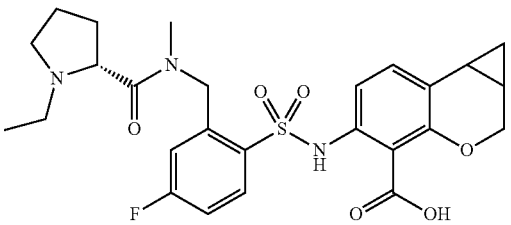
Second eluting enantiomer: retention time on above column 35.51 minutes, >99% ee

^{1}H NMR (DMSO-d_6) δ: 7.65 (1H, dd), 7.60 (1H, td), 7.43-7.38 (2H, m), 7.28 (1H, d), 7.08 (1H, d), 6.95 (1H, d), 6.16-6.07 (1H, m), 4.16 (1H, d), 3.77-3.67 (2H, m), 3.56 (1H, d), 3.09 (4H, q), 1.91 (1H, dt), 1.71 (1H, q), 1.12 (6H, t), 0.93 (1H, dt), 0.72 (1H, q).

LCMS (Method C) r/t 3.20 (M+H) 457.

Example 65

(1aRS,7bSR)-5-(2-{N—[((R)-1-Ethylpyrrolidine-2-yl)carbonyl]-N-methylamino-methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



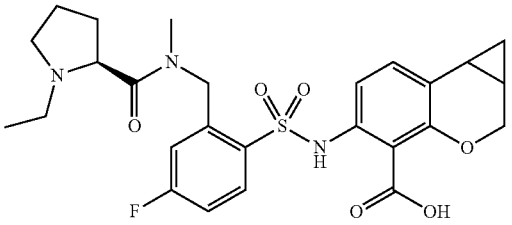
A mixture of methyl (1aRS,7bSR)-5-(2-{N—[((R)-1-ethylpyrrolidine-2-yl)carbonyl]-N-methyl-aminomethyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 155, 0.177 g) and lithium hydroxide monohydrate (0.136 g) in dioxane (5 mL) and water (2 mL) was stirred and heated at 100° C. for 19.5 hours. After cooling, the mixture was evaporated to dryness and the residue was acidified by addition of aqueous citric acid solution (10%). The resultant solid was collected by filtration, washed with water and dried under vacuum at 40° C. The solid was purified by preparative HPLC (C18) eluting with a mixture of methanol and water, containing 0.1% formic acid, with a gradient of 10-98% to give (1aRS, 7bSR)-5-(2-{N—[((R)-1-ethylpyrrolidine-2-yl)carbonyl]-N-methylaminomethyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.053 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.93-7.78 (1H, m), 7.17 (1H, m), 6.99 (0.5H, m), 6.95 (0.5H, d), 6.90-6.76 (1.5H, m), 6.69 (0.5H, dd), 5.02 (1.5H, m), 4.86 (0.5H, dd), 4.61-4.44 (1H, br s), 4.15 (1H, dd), 3.55 (3H, m), 3.11 (2H, m), 2.90 (3H, 2s), 2.06-1.54 (6H, m), 1.18-1.05 (4H, m), 0.84 (1H, m), 0.68 (1H, m).

LCMS (Method C) r/t 3.14 (M+H) 532.

Example 66

(1aRS,7bSR)-5-(2-{N—[((S)-1-Ethylpyrrolidine-2-yl)carbonyl]-N-methylamino-methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



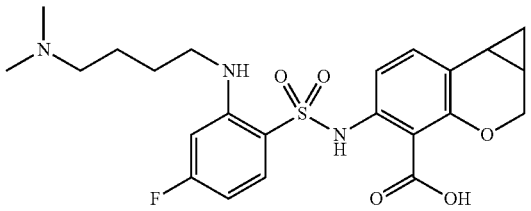
Prepared by proceeding in a similar manner to Example 65, starting from methyl (1aRS,7bSR)-5-(2-{N—[((S)-1-ethylpyrrolidine-2-yl)carbonyl]-N-methylaminomethyl}-4-fluorobenzene-sulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 160) as a white solid.

^{1}H NMR (DMSO-d_6) 7.94-7.76 (1H, m), 7.18 (1H, m), 7.02-6.92 (1H, m), 6.92-6.76 (1.5H, m), 6.68 (0.5H, m), 5.02 (1.5H, m), 4.86 (0.5H, dd), 4.65-4.49 (1H, br s), 4.15 (1H, dd), 3.55 (3H, m), 3.14 (2H, m), 2.91 (3H, 2s), 2.07-1.59 (6H, m), 1.13 (4H, m), 0.85 (1H, m), 0.68 (1H, m).

LCMS (Method C) r/t 3.15 (M+H) 532.

Example 67

(1aRS,7bSR)-5-[2-(4-Dimethylaminobutylamino)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



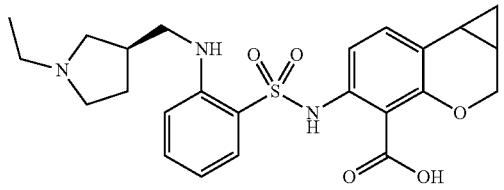
A mixture of methyl (1aRS,7bSR)-5-[2-(4-dimethylaminobutylamino)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 161, 0.485 g) and lithium hydroxide monohydrate (0.505 g) in dioxane (9 mL) and water (3 mL) was irradiated in the microwave at 130° C. for 45 minutes. After cooling, the mixture was diluted with methanol, acidified with formic acid and evaporated in vacuo. The residue was triturated with 20% methanol in DCM, filtered and the filtrate was evaporated in vacuo. The residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-20%. The resultant solid was triturated with ethyl acetate and filtered off to give (1aRS,7bSR)-5-[2-(4-dimethylaminobutylamino)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (0.215 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 12.52 (2H, br, s), 7.65 (1H, dd), 7.08 (2H, q), 6.56 (1H, dd), 6.39 (1H, dt), 5.98 (1H, m), 4.20 (1H, d), 3.59 (1H, d), 3.22 (2H, q), 2.98 (2H, m), 2.75 (6H, s), 1.91 (1H, m), 1.81 (2H, m), 1.72 (1H, m), 1.58 (2H, m), 0.92 (1H, m), 0.76 (1H, m).

LCMS (Method C) r/t 3.43 (M+H) 478.

Example 68

(1aRS,7bSR)-5-{2-[((R)-1-Ethylpyrrolidin-3-ylmethyl)amino]benzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



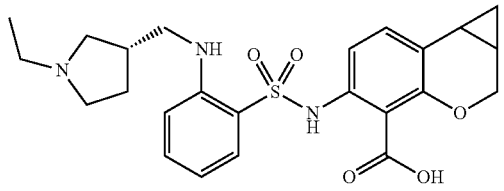
A solution of (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (Intermediate 67, 0.105 g), ((R)-1-ethylpyrrolidin-3-yl)methyl-amine (Intermediate 163, 0.5 g) and triethylamine (0.5 g) in DMSO (1 mL) was stirred and heated at 140° C. overnight. After cooling, the mixture was concentrated under vacuum and the residue was purified by chromatogrpahy on silica, eluting with a mixture of methanol and DCM (5%). The product was purified by HPLC (C18) to give (1aRS,7bSR)-5-{2-[((R)-1-ethylpyrrolidin-3-ylmethyl) amino]benzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]-chromene-4-carboxylic acid (0.03 g) as a white solid,

^{1}H NMR (DMSO-d_6) δ: 7.38 (1H, dd), 7.24 (1H, t), 7.06 (2H, s), 6.81 (1H, d), 6.49 (1H, t), 6.14 (1H, br s), 4.13 (1H, dd), 3.54 (2H, m), 3.25 (2H, m) 3.07 (4H, m), 2.82 (1H, m), 2.63 (1H, m), 1.96 (1H, m), 1.86 (1H, m), 1.71-1.46 (2H, m), 1.19 (3H, m), 0.87 (1H, m), 0.70 (1H, m).

LCMS (Method C) r/t 3.31 (M+H) 472.

Example 69

(1aRS,7bSR)-5-{2-[((S)-1-Ethylpyrrolidin-3-ylmethyl)amino]benzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



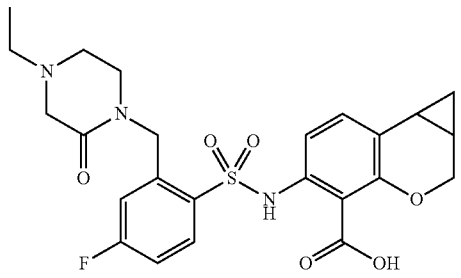
A solution of (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic (Intermediate 67, 0.08 g), and ((S)-1-ethylpyrrolidin-3-yl)methylamine (Intermediate 169, 0.8 g) in DMSO (0.2 mL) was stirred and heated at 120° C. for 24 hours. After cooling, the mixture was diluted with methanol and concentrated under vacuum. The residue was purified by HPLC (C18) to give (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-3-ylmethyl)amino]benzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]-chromene-4-carboxylic acid (0.03 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.37 (1H, dd), 7.24 (1H, t), 7.05 (2H, s), 6.80 (1H, d), 6.48 (1H, t), 6.13 (1H, br s), 4.13 (1H, dd), 3.54 (2H, m), 3.24 (2H, m), 3.05 (4H, m), 2.82 (1H, m), 2.62 (1H, m), 1.95 (1H, m), 1.85 (1H, m), 1.71-1.46 (2H, m), 1.18 (3H, m), 0.86 (1H, m), 0.69 (1H, m).

LCMS (Method C) r/t 3.25 (M+H) 472.

Example 70

(1aRS,7bSR)-5-[2-(4-Ethyl-2-oxopiperazin-1-ylmethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



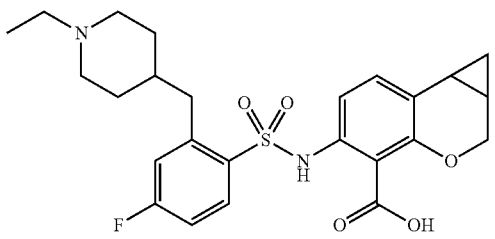
A mixture of methyl (1aRS,7bSR)-5-[2-(4-ethyl-2-oxopiperazin-1-ylmethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 173, 0.28 g) and lithium hydroxide monohydrate (0.126 g) in dioxane (9 mL) and water (3 mL) was irradiated in the microwave at 130° C. for 30 minutes. After cooling, the mixture was diluted with methanol, acidified with formic acid and evaporated in vacuo. The residue was triturated with 20% methanol in DCM, filtered and the filtrate was evaporated in vacuo. The residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-20%. The resultant solid was triturated with ether and filtered to give (1aRS,7bSR)-5-[2-(4-ethyl-2-oxo-piperazin-1-ylmethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c] chromene-4-carboxylic acid (0.176 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 11.28 (1H, br, s), 8.02 (1H, dd), 7.31 (1H, d), 7.23 (1H, d), 6.98 (2H, m), 4.98 (2H, q), 4.57 (1H, d), 4.04 (1H, d), 3.36 (2H, t), 3.30 (2H, s), 2.72 (2H, t), 2.51 (2H, q), 1.96 (1H, m), 1.80 (1H, m), 1.11 (4H, m), 1.03 (1H, m).

LCMS (Method C) r/t 2.96 (M+H) 504.

Example 71

(1aRS,7bSR)-5-[2-(1-Ethylpiperidin-4-ylmethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



Methyl (1aRS,7bSR)-5-[2-(1-ethylpiperidin-4-ylmethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 177, 0.279 g)

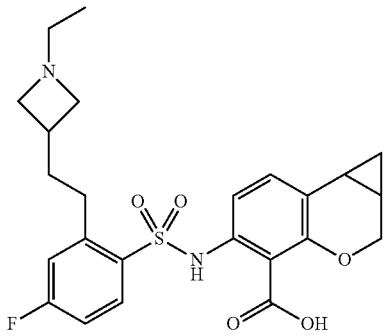
and lithium hydroxide monohydrate (0.233 g) were suspended in dioxane (7 mL) and water (3 mL) and the mixture was stirred and heated at 80° C. for 25 hours. Further lithium hydroxide monohydrate (0.116 g) was added and the mixture heating was continued for 18 hours. After cooling, the volatiles were removed in vacuo, the residue was acidified by addition of aqueous citric acid solution (10%) and saturated with sodium chloride. The mixture was extracted with DCM and the organic layer was dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by preparative HPLC (C18), eluting with a mixture of methanol and water, containing 0.1% formic acid, with a gradient of 10-98% to give (1aRS,7bSR)-5-[2-(1-ethylpiperidin-4-ylmethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.117 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.99 (1H, dd), 7.22-7.14 (2H, m), 6.99 (1H, d), 6.76 (1H, d), 4.20 (1H, d), 3.60 (1H, d), 3.34 (2H, d), 3.02-2.88 (4H, m), 2.71 (2H, br s), 1.99 (1H, br s), 1.84 (1H, dt), 1.74-1.62 (3H, m), 1.56-1.40 (2H, m), 1.18 (3H, t), 0.89 (1H, dt), 0.73 (1H, q).

LCMS (Method C) r/t 3.22 (M+H) 489.

Example 72

(1aRS,7bSR)-5-{2-[2-(1-Ethylazetidin-3-yl)ethyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



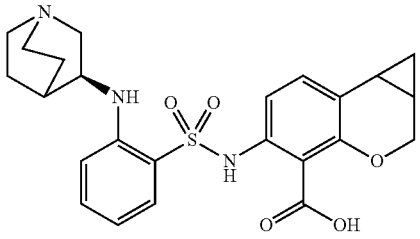
A mixture of methyl (1aRS,7bSR)-5-{2-[2-(1-ethylazetidin-3-yl)ethyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (intermediate 183, 0.306 g) and lithium hydroxide monohydrate (0.421 g) in dioxane (7.5 mL) and water (2.5 mL) was irradiated in the microwave at 130° C. for 45 minutes. After cooling, the mixture was diluted with methanol, acidified with formic acid and evaporated in vacuo. The residue was triturated with 20% methanol in DCM, filtered and the filtrate was evaporated in vacuo. The residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-30%. The resultant solid was triturated with ether and filtered to give (1aRS,7bSR)-5-{2-[2-(1-ethyl-azetidin-3-yl)ethyl]-4-fluorbenzenesulfonylamino}1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.241 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.92 (1H, br, s), 7.35 (1H, dd), 7.22 (1H, dt), 7.17 (1H, d), 6.78 (1H, br, s), 4.27 (1H, d), 4.05 (2H, m), 3.78 (2H, br, s), 3.70 (1H, d), 3.17 (2H, q), 2.86 (2H, br, s), 2.70 (1H, br, s), 1.95 (1H, m), 1.84 (2H, m), 1.75 (1H, m), 1.11 (3H, t), 0.98 (1H, m), 0.76 (1H, m).

LCMS (Method C) r/t 3.36 (M+H) 475.

Example 73

(1aRS,7bSR)-5-{2-[((S)-1-Azabicyclo[2.2.2]oct-3-yl)amino]benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



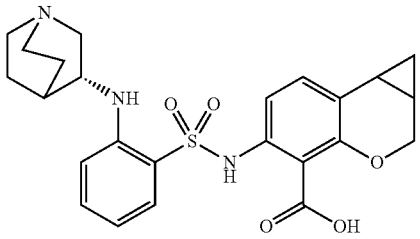
A solution of (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (Intermediate 67, 0.6 g) and (S)-1-azabicyclo [2.2.2]oct-3-ylamine (6.0 g) in DMSO (6 mL) was stirred and heated in a sealed vessel at 140° C. for 22 hours. After cooling, the mixture was diluted with methanol and concentrated under vacuum. The residue was purified by HPLC (C18) to give (1aRS,7bSR)-5-{2-[((S)-1-azabicyclo[2.2.2]oct-3-yl) amino]benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.107 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.58 (1H, ddd), 7.25 (1H, t), 6.94 (1H, dd), 6.76 (2H, t), 6.62 (2H, m), 6.06 (1H, d), 4.14 (1H, t), 3.86 (1H, br s), 3.57 (3H, m), 3.16-2.87 (4H, m), 2.12 (1H, m), 2.01 (1H, m), 1.82 (3H, m), 1.65 (2H, m), 0.83 (1H, m), 0.67 (1H, m).

LCMS (Method C) r/t 3.16 (M+H) 470).

Example 74

(1aRS,7bSR)-5-{2-[((R)-1-Azabicyclo[2.2.2]oct-3-yl)amino]benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



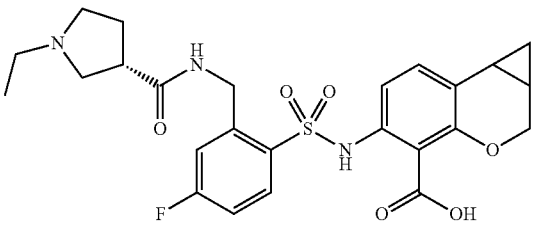
Prepared by proceeding in a similar manner to Example 73, starting from (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (Intermediate 67) and (R)-1-azabicyclo [2.2.2]oct-3-ylamine.

^{1}H NMR (DMSO-d_6) δ: 7.58 (1H, ddd), 7.25 (1H, t), 6.94 (1H, dd), 6.76 (2H, t), 6.62 (2H, m), 6.07 (1H, d), 4.13 (1H, t), 3.86 (1H, br s), 3.57 (3H, m), 3.16-2.87 (4H, m), 2.12 (1H, m), 2.01 (1H, m), 1.83 (3H, m), 1.64 (2H, m), 0.83 (1H, m), 0.67 (1H, m).

LCMS (Method C) r/t 3.15 (M+H) 470

Example 75

(1aRS,7bSR)-5-(2-{[((S)-1-ethylpyrrolidine-3-carbonyl)amino]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



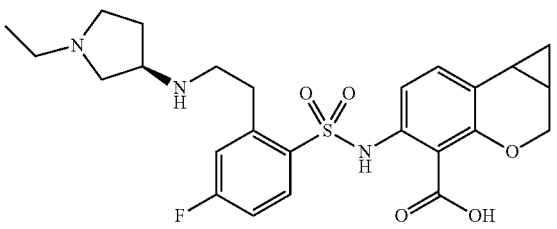
Methyl (1aRS,7bSR)-5-(2-{[((S)-1-ethylpyrrolidine-3-carbonyl)amino]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 188, 0.190 g) and lithium hydroxide monohydrate (0.150 g) were suspended in dioxane (5 mL) and water (5 mL) and the mixture was stirred and heated at 100° C. for 18.5 hours. After cooling, the volatiles were removed in vacuo and the residue was acidified by addition of aqueous citric acid solution (10%) and extracted with DCM. The organic layer was dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by preparative HPLC (C18) eluting with a mixture of acetonitrile and water, containing 0.1% formic acid, with a gradient of 25-60% to give (1aRS,7bSR)-5-(2-{[((S)-1-ethylpyrrolidine-3-carbonyl)amino]methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.092 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 8.78 (1H, q), 7.89-7.82 (1H, m), 7.19 (1H, td), 7.12 (1H, dt), 7.02 (1H, dd), 6.75 (1H, dd), 4.74 (2H, d), 4.19 (1H, d), 3.62 (1H, dt), 3.50-3.15 (5H, m), 3.10 (2H, q), 2.35-2.23 (1H, m), 2.10-1.99 (1H, m), 1.86 (1H, dt), 1.75-1.67 (1H, m), 1.20 (3H, t), 0.90 (1H, dt), 0.73 (1H, q)

LCMS (Method C) r/t 3.01 (M+H) 518

Example 76

(1aRS,7bSR)-5-{2-[2-((R)-1-Ethylpyrrolidin-3-ylamino)ethyl]-4-fluoro-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



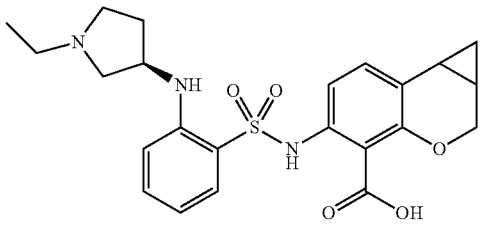
A solution of (1aRS,7bSR)-5-(4-fluoro-2-vinylbenzenesulfonylamino)-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid (Intermediate 74, 0.150 g) and (R)-1-ethylpyrrolidin-3-ylamine (Intermediate 193, 0.25 g) in ethylene glycol (1 ml) was irradiated in the microwave at 200° C. for 30 minutes. After cooling, the mixture was diluted with water and loaded onto a SCX-2 SPE cartridge then washed with water, methanol and 2M ammonia in methanol. The basic fractions were combined and evaporated to dryness. The residue was purified by preparative HPLC (C18) eluting with a mixture of methanol and water, containing 0.1% ammonia, with a gradient of 10-98%. Then further purified by preparative HPLC (C18) eluting with a mixture of acetonitrile and water, containing 0.1% formic acid, with a gradient of 10-60% to give (1aRS,7bSR)-5-{2-[2-((R)-1-ethylpyrrolidin-3-ylamino)ethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid (0.005 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 7.86 (1H, dd), 7.43 (1H, dd), 7.31 (1H, dt), 7.27 (1H, d), 6.59 (1H, d), 4.31 (1H, d), 4.18-3.97 (1.5H, br), 3.82-3.64 (1.5H, br), 3.79 (1H, d), 3.33-3.20 (8H, br), 2.31 (1H, br s), 2.04 (1H, m), 1.84 (1H, q), 1.26 (4H, t), 1.07 (1H, m), 0.86 (1H, q).

LCMS (Method C) r/t 2.60 (M+H) 503.9

Example 77

(1aRS,7bSR)-5-{2-[((R)-1-Ethylpyrrolidin-3-yl)amino]benzenesulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid



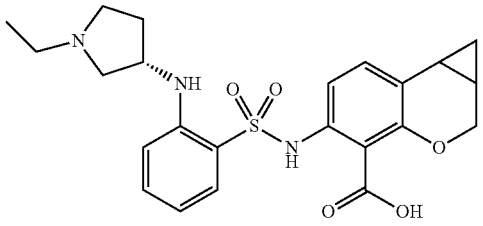
A solution of (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (Intermediate 67, 0.13 g) and (R)-1-ethylpyrrolidin-3-ylamine (Intermediate 193, 1.22 g) in DMSO (0.7 mL) was stirred and heated in a sealed vessel at 120° C. for 22 hours. After cooling, the mixture was diluted with methanol and concentrated under vacuum. The residue was purified by HPLC (C18) to give (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-3-yl)amino]benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.107 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.32 (2H, m), 7.04 (1H, d), 6.98 (1H, m), 6.72 (1H, d), 6.60 (1H, t), 5.55 (1H, br s), 4.18 (1H, br s), 4.11 (1H, t), 3.78 (1H, br s), 3.66-3.48 (2H, m), 3.18-2.94 (4H, m), 2.54 (1H, m), 1.86 (2H, m), 1.66 (1H, m), 1.22 (3H, t), 0.86 (1H, m), 0.68 (1H, m).

LCMS (Method C) r/t 3.40 (M+H) 458.

Example 78

(1aRS,7bSR)-5-{2-[((S)-1-Ethylpyrrolidin-3-yl) amino]benzenesulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid



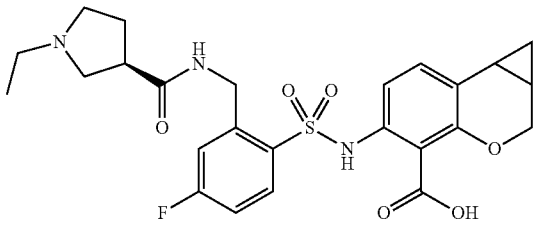
Prepared by proceeding in a similar manner to Example 77, starting from (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (Intermediate 67) and (S)-1-ethylpyrrolidin-3-ylamine (Intermediate 194).

^{1}H NMR (DMSO-d_6) δ: 7.32 (2H, m), 7.05 (1H, d), 6.98 (1H, m), 6.72 (1H, d), 6.60 (1H, t), 5.54 (1H, br s), 4.20 (1H, br s), 4.11 (1H, t), 3.80 (1H, br s), 3.69-3.48 (2H, m), 3.19-2.96 (4H, m), 2.56 (1H, m), 1.86 (2H, m), 1.66 (1H, m), 1.22 (3H, t), 0.87 (1H, m), 0.68 (1H, m).

LCMS (Method C) r/t 3.40 (M+H) 458.

Example 79

(1aRS,7bSR)-5-(2-{[(R)-1-Ethylpyrrolidine-3-yl-carbonyl)amino]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylic acid



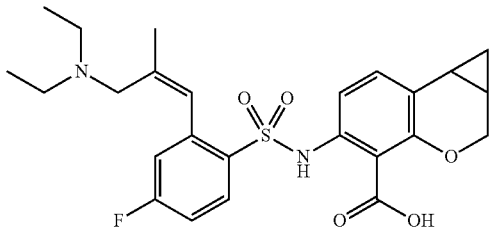
A mixture of methyl (1aRS,7bSR)-5-(2-{[((R)-1-ethylpyrrolidine-3-ylcarbonyl)amino]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylate (Intermediate 195, 0.215 g) and lithium hydroxide monohydrate (0.170 g) was suspended in dioxane (5 mL) and water (5 mL) and the mixture was stirred and heated at 80° C. for 21 hours. The temperature was raised to 100° C. and the mixture was stirred and heated at that temperature for 2.5 hours. Further lithium hydroxide monohydrate (0.05 g) was added and the mixture was stirred and heated at 100° C. for 2 hours. After cooling, the volatiles were removed in vacuo and the residue was acidified by addition of aqueous citric acid solution (10%) and extracted with DCM. The organic layer was dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by preparative HPLC (C18) eluting with a mixture of acetonitrile and water, containing 0.1% formic acid, with a gradient of 25-60% to give (1aRS,7bSR)-5-(2-{[((R)-1-ethylpyrrolidine-3-ylcarbonyl)-amino]methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.103 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 8.78 (1H, q), 7.89-7.83 (1H, m), 7.18 (1H, td), 7.11 (1H, dt), 7.01 (1H, dd), 6.76 (1H, dd), 4.74 (2H, d), 4.19 (1H, d), 3.61 (1H, dt), 3.46-3.12 (5H, m), 3.07 (2H, q), 2.34-2.22 (1H, m), 2.10-1.98 (1H, m), 1.86 (1H, dt), 1.70 (1H, q), 1.19 (3H, t), 0.90 (1H, dt), 0.73 (1H, q).

LCMS (Method C) r/t 3.04 (M+H) 518.

Example 80

(1aRS,7bSR)$_5$-[2-((Z)-3-Diethylamino-2-methyl-prop-1-enyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



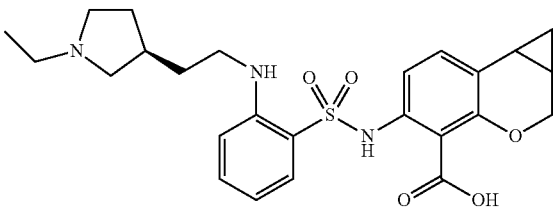
A mixture of methyl (1aRS,7bSR)-5-[N-[2-((Z)-3-diethylamino-2-methylprop-1-enyl)-4-fluorobenzenesulfonyl]-N-methoxycarbonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 200, 0.264 g) and lithium hydroxide monohydrate (0.505 g) in dioxane (9 mL) and water (3 mL) was irradiated in the microwave at 130° C. for 40 minutes. After cooling, the mixture was diluted with methanol, acidified with formic acid and evaporated in vacuo then azeotroped with a mixture of ethanol and toluene. The residue was triturated with 15% methanol in DCM, filtered and the filtrate was evaporated in vacuo. The residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-40%. The resultant solid was triturated with ether and filtered to give (1aRS, 7bSR)-5-[2-((Z)-3-diethylamino-2-methylprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclo-propa[c]chromene-4-carboxylic acid (0.202 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.95 (1H, dd), 7.28 (1H, dt), 7.14 (1H, dd), 7.06 (1H, d), 6.92 (1H, s), 6.64 (1H, d), 4.25 (1H, d), 3.64 (1H, d), 3.36 (2H, br, s), 2.63 (4H, q), 1.96 (3H, s), 1.90 (1H, m), 1.74 (1H, m), 0.93 (1H, m), 0.86 (6H, t), 0.75 (1H, m).

LCMS (Method C) r/t 3.27 (M+H) 489

Example 81

(1aRS,7bSR)-5-{2-[2-((R)-1-Ethylpyrrolidin-3-yl) ethylamino]benzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



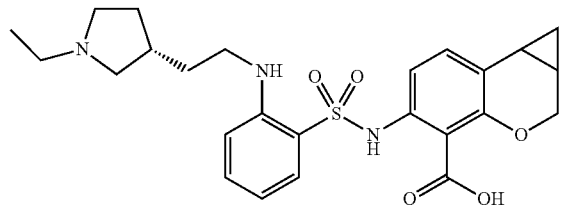
A mixture of (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (Intermediate 67, 0.2 g) and 2-((R)-1-ethylpyrrolidin-3-yl)ethylamine (Intermediate 203, 2.0 g) in DMSO (2 mL) was divided between two sealed vials and each was stirred and heated at 130° C. for 24 hours. After cooling, the combined mixture was diluted with methanol and then concentrated under vacuum. The residue was purified by HPLC (C18) to give (1aRS,7bSR)-5-{2-[2-((R)-1-ethylpyrrolidin-3-yl)ethylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.125 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.62 (1H, dt), 7.29 (1H, dt), 7.02 (2H, 2s), 6.70 (1H, d), 6.58 (1H, t), 5.84 (1H, br m), 4.14 (1H, d), 3.54 (1H, d), 3.36 (1H m), 3.18 (3H, m), 3.06 (4H, m), 2.59 (1H, m), 2.01 (1H, m), 1.83 (1H, m), 1.80-1.49 (4H, m), 1.19 (3H, q), 0.85 (1H, m), 0.69 (1H, m).

LCMS (Method C) r/t 3.35 (M+H) 486.

Example 82

(1aRS,7bSR)-5-{2-[2-((S)-1-Ethylpyrrolidin-3-yl) ethylamino]benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



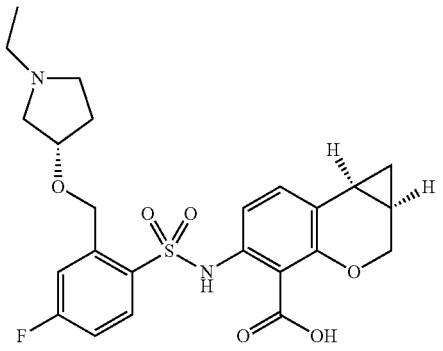
Prepared by proceeding in a similar manner to Example 58, starting from (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (Intermediate 67) and 2-((S)-1-ethylpyrrolidin-3-yl)ethylamine (Intermediate 208).

^{1}H NMR (DMSO-d_6) δ: 7.62 (1H, dt), 7.29 (1H, dt), 7.02 (2H, 2s), 6.70 (1H, d), 6.57 (1H, t), 5.84 (1H, br m), 4.14 (1H, d), 3.54 (1H, d), 3.36 (1H m), 3.17 (3H, m), 3.06 (4H, m), 2.57 (1H, m), 2.01 (1H, m), 1.83 (1H, m), 1.80-1.49 (4H, m), 1.19 (3H, q), 0.85 (1H, m), 0.68 (1H, m).

LCMS (Method C) r/t 3.34 (M+H) 486.

Example 83

(1aR,7bS)-5-[2-((S)-1-Ethylpyrrolidin-3-yloxymethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



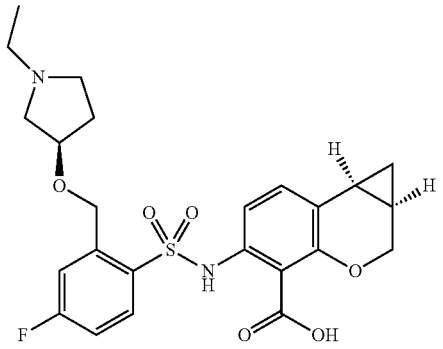
A mixture of methyl (1aR,7bS)-5-[2-((S)-1-ethylpyrrolidin-3-yloxymethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 213, 0.217 g) and lithium hydroxide monohydrate (0.168 g) in dioxane (3 mL) and water (1 mL) was irradiated in the microwave at 130° C. for 40 minutes. After cooling, the mixture was diluted with methanol, acidified with formic acid, evaporated in vacuo and azeotroped with a mixture of toluene and ethanol. The residue was triturated with 15% methanol in DCM, filtered and the filtrate was evaporated in vacuo. The residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-20%. The resultant gum was triturated with ether and ethyl acetate and filtered to give (1aR,7bS)-5-[2-((S)-1-ethylpyrrolidin-3-yloxymethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.136 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 7.35 (1H, dd), 7.23 (1H, d), 7.19 (1H, dd), 7.01 (1H, d), 6.83 (1H, dt), 4.87 (1H, br, d), 4.73 (1H, br, d), 4.36 (2H, br, m), 4.19 (1H, d), 3.88 (1H, m), 3.84 (1H, d), 3.38 (1H, m), 2.94 (1H, m), 2.86 (1H, m), 2.75 (1H, m), 2.26-2.45 (2H, m), 1.81 (1H, m), 1.60 (1H, m), 1.39 (3H, t), 0.90 (2H, m).

LCMS (Method C) r/t 3.25 (M+H) 491

Example 84

(1aR,7bS)-5-[2-((R)-1-Ethylpyrrolidin-3-yloxymethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



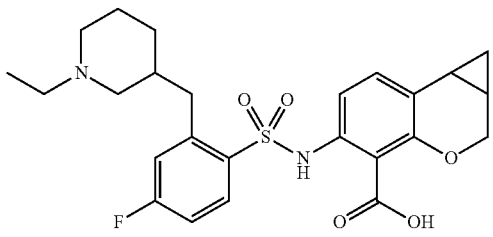
Prepared by proceeding in a similar manner to Example 83, starting from methyl (1aR,7bS)-5-[2-((R)-1-ethylpyrrolidin-3-yloxymethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (Intermediate 217).

^{1}H NMR (DMSO-d_6) δ: 7.83 (1H, dd), 7.44 (1H, dd), 7.20 (1H, dt), 7.07 (1H, d), 7.03 (1H, d), 4.99 (1H, d), 4.49 (2H, d), 4.19 (2H, d), 3.57 (2H, d), 2.93-3.30 (4H, m), 2.34 (1H, m), 2.13 (1H, m), 1.88 (1H, m), 1.72 (1H, m), 1.29 (3H, t), 0.92 (1H, m), 0.75 (1H, m).

LCMS (Method C) r/t 3.25 (M+H) 491.

Example 85

(1aR,7bS)-5-[2-(1-Ethylpiperidin-3-ylmethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



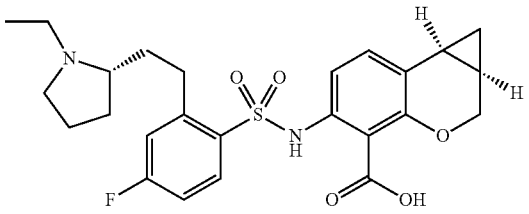
A mixture of methyl (1aR,7bS))-5-[2-(1-ethylpiperidin-3-ylmethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 221, 0.071 g) and lithium hydroxide monohydrate (0.059 g) was suspended in dioxane (5 mL) and water (2 mL) and the mixture was stirred and heated at 100° C. for 25 hours. Further lithium hydroxide monohydrate (0.116 g) was added and the mixture was heated at 100° C. for a further 18 hours. After cooling, the volatiles were removed in vacuo and the residue was acidified by addition of aqueous citric acid solution (10%) and saturated with sodium chloride. The mixture was extracted with DCM and the organic layer was dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by preparative HPLC (C18), eluting with a mixture of acetonitrile and water, containing 0.1% formic acid, with a gradient of 25-60% to give (1aR,7bS)-5-[2-(1-ethyl-piperidin-3-ylmethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (0.032 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 8.01-7.91 (1H, m), 7.26-7.18 (2H, m), 7.10-7.00 (2H, m), 4.22-4.17 (1H, m), 3.61 (1H, d), 3.45-2.92 (5H, m), 3.02-2.88 (4H, m), 1.94-1.85 (1H, m), 1.80-1.65 (3H, m), 1.65-1.50 (1H, m), 1.30-1.14 (4H, m), 0.97-0.87 (1H, m), 0.77-0.68 (1H, m).

LCMS (Method C) r/t 3.21 (M+H) 489.

Example 86

(1aR,7bS)-5-{2-[2-((R)-1-Ethylpyrrolidin-2-yl) ethyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid



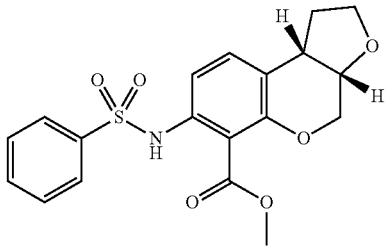
Lithium hydroxide (0.22 g) was added to a solution of methyl (1aR,7bS)-5-{2-[2-((R)-1-ethyl-pyrrolidin-2-yl) ethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 229, 0.26 g) in a mixture of dioxane (12 mL) and water (4 mL) and the mixture was irradiated in a microwave at 150° C. for 20 minutes. After cooling, the mixture was evaporated to dryness and the residue was acidified by addition of 10% aqueous citric acid (3 mL) and then extracted with DCM. The organic layer was dried ($MgSO_4$) and filtered and the filtrate was evaporated to dryness. The residue was purified by preparative HPLC (C18) eluting with a mixture of acetonitrile and water, containing 0.1% formic acid, with a gradient of 25-35% to give (1aR,7bS)-5-{2-[2-((R)-1-ethylpyrrolidin-2-yl)ethyl]-4-fluoro-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.11 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.88 (1H, dd), 7.33 (1H, dd), 7.15 (1H, dt), 7.08 (1H, d), 6.98 (1H, d), 4.18 (1H, d), 3.68 (1H, br m), 3.58 (1H, d), 3.56 (1H, m), 3.22-2.96 (5H, m), 2.23 (1H, m), 2.03 (4H, m), 1.87 (2H, m), 1.72 (1H, q), 1.31 (3H, t), 0.91 (1H, m), 0.72 (1H, q).

LCMS (Method C) r/t 3.24 (M+H) 489.

Intermediate 1

Methyl cis-(3aRS,9bRS)-7-(benzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate



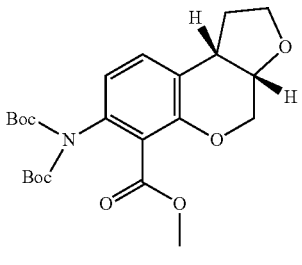
Mixture of cis enantiomers

Formic acid (5 mL) was added to methyl cis-(3aRS,9bRS)-7-[bis-(tert-butoxycarbonyl)amino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (Intermediate 2, 0.15 g) and the mixture was stirred at room temperature for 1 hour. The resultant mixture was evaporated to dryness and the residue was redissolved in toluene and evaporated to dryness three times. The residue was dissolved in DCM (2 mL) and pyridine (1 mL) was added followed by benzenesulfonyl chloride (0.07 g). The resultant mixture was stirred at room temperature for 90 minutes then diluted with DCM and washed with sodium hydroxide (1M) and brine. The sodium hydroxide washing was saturated with salt and then extracted with ethyl acetate, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give methyl cis-(3aRS,9bRS)-7-(benzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (0.082 g) as a gum.

^{1}H NMR ($CDCl_3$) δ: 7.73 (2H, dd), 7.53 (1H, t), 7.42 (2H, t), 7.25 (1H, d), 7.21 (1H, d), 4.29 (1H, m), 4.03 (1H, dd), 3.93 (1H, dd), 3.82 (2H, t), 3.70 (3H, s), 3.45 (1H, m), 2.48 (1H, m), 1.87 (1H, m).

Intermediate 2

Methyl cis-(3aRS,9bRS)-7-[bis-(tert-butoxycarbonyl)amino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate



Mixture of cis enantiomers

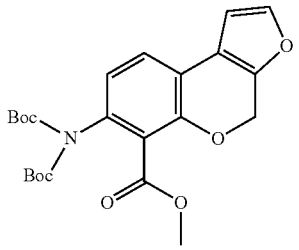
A solution of methyl 7-[bis-(tert-butoxycarbonyl)amino]-4H-furo[2,3-c]-chromene-6-carboxylate (Intermediate 3, 0.15 g) in a mixture of dioxane (15 mL) and acetic acid (1.5 mL) was treated under an atmosphere of nitrogen with palladium on carbon (10%, 0.02 g). The mixture was stirred and the nitrogen was replaced by hydrogen then the mixture was stirred under an atmosphere of hydrogen for 3 hours. The mixture was filtered through Celite, the pad was washed

thoroughly with dioxane and the filtrate was evaporated to dryness to give methyl cis-(3aRS,9bRS)-7-[bis-(tert-butoxycarbonyl)amino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (0.15 g) as a gum.

^{1}H NMR ($CDCl_3$) δ: 7.22 (1H, dd), 6.80 (1H, d), 4.36 (1H, m), 4.07 (2H, d), 3.86 (2H, t), 3.84 (3H, s), 3.53 (1H, m), 2.50 (1H, m), 1.94 (1H, m), 1.40 (18H, s).

Intermediate 3

Methyl 7-[bis-(tert-butoxycarbonyl)amino]-4H-furo[2,3-c]-chromene-6-carboxylate

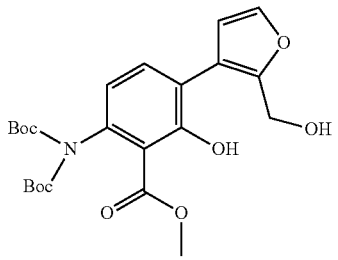


Carbon tetrabromide (2.66 g) was added to a solution of methyl 6-[bis-(tert-butoxycarbonyl)amino]-2-hydroxy-3-(2-hydroxymethylfuran-3-yl)-benzoate (Intermediate 4, 2.65 g) and triphenyl phosphine (2.1 g) in DCM (40 mL) and the resultant solution was stirred at room temperature for 1 hour. The mixture was evaporated to dryness and DMF (60 mL) and cesium carbonate (5.59 g) were added to the residue. The resultant mixture was stirred for 1 hour, then partitioned between ethyl acetate and water. The organic layer was separated, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 5-25% to give methyl 7-[bis-(tert-butoxycarbonyl)amino]-4H-furo[2,3-c]-chromene-6-carboxylate (0.735 g) as a gum which crystallised on standing.

^{1}H NMR ($CDCl_3$) δ: 7.45 (1H, m), 7.26 (1H, s), 6.79 (1H, d), 6.65 (1H, d), 5.44 (2H, s), 3.87 (3H, s), 1.42 (18H, s).

Intermediate 4

Methyl 6-[bis-(tert-butoxycarbonyl)amino]-2-hydroxy-3-(2-hydroxymethylfuran-3-yl)benzoate

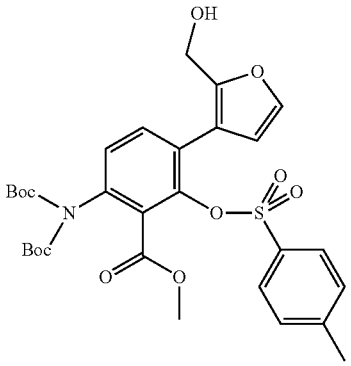


1M aqueous sodium hydroxide (50 mL) was added to a solution of methyl 6-[bis-(tert-butoxycarbonyl)amino]-3-(2-hydroxymethylfuran-3-yl)-2-(4-methylbenzene-sulfonyloxy)benzoate (Intermediate 5, 3.82 g) in methanol (100 mL) and the mixture was stirred and heated at 45° C. for 1.5 hours. The mixture was evaporated to dryness and the residue was dissolved in ethyl acetate and acidified with acetic acid. The organic layer was separated, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 10-50% to give methyl 6-[bis-(tert-butoxycarbonyl)amino]-2-hydroxy-3-(2-hydroxymethylfuran-3-yl)benzoate (2.65 g) as a white foam.

^{1}H NMR ($CDCl_3$) δ: 11.91 (1H, s), 7.50 (2H, m), 6.80 (1H, d), 6.57 (1H, d), 4.58 (2H, s), 3.97 (3H, s), 1.43 (18H, s).

Intermediate 5

Methyl 6-[bis-(tert-butoxycarbonyl)amino]-3-(2-hydroxymethyl-furan-3-yl)-2-(4-methylbenzene-sulfonyloxy)benzoate

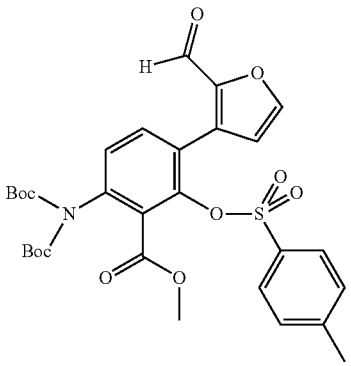


Sodium borohydride (0.304 g) was added to a solution of methyl 6-[bis-(tert-butoxycarbonyl)amino]-3-(2-formylfuran-3-yl)-2-(4-methylbenzenesulfonyloxy)-benzoate (Intermediate 6, 3.9 g) in ethanol (50 mL) and the mixture was stirred for 15 minutes. The mixture was evaporated to dryness and the residue was partitioned between ethyl acetate and water. The organic layer was separated, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give methyl 6-[bis-(tert-butoxycarbonyl)amino]-3-(2-hydroxymethylfuran-3-yl)-2-(4-methylbenzene-sulfonyloxy)benzoate (3.82 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 7.40 (1H, d), 7.38 (2H, d), 7.30 (1H, d), 7.18 (1H, d), 7.11 (2H, d), 6.28 (1H, d), 4.33 (2H, s), 3.82 (3H, s), 2.40 (3H, s), 1.42 (18H, s).

Intermediate 6

Methyl 6-[bis-(tert-butoxycarbonyl)amino]-3-(2-formylfuran-3-yl)-2-(4-methylbenzenesulfonyloxy)benzoate

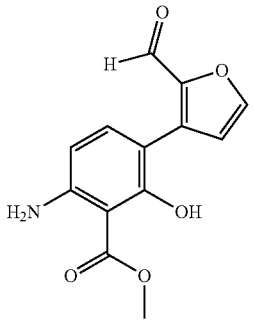


Triethylamine (0.848 g) was added to a stirred solution of methyl 6-amino-3-(2-formylfuran-3-yl)-2-hydroxybenzoate (Intermediate 7, 1.72 g), 4-methylbenzenesulfonyl chloride (1.25 g) and DMAP (0.804 g) in DCM (30 mL) and the resultant mixture was stirred for 1 hour. The mixture was diluted with water and the organic layer was separated, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was dissolved in acetonitrile (30 mL) and DMAP (0.804 g) and di-tert-butyl dicarboante (3.16 g) were added. The mixture was stirred for 2 hours then diluted with ethyl acetate and water. The organic layer was separated, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 10-50% to give methyl 6-[bis-(tert-butoxycarbonyl)amino]-3-(2-formylfuran-3-yl)-2-(4-methylbenzenesulfonyloxy)-benzoate (3.91 g) as a white foam.

^{1}H NMR ($CDCl_3$) δ: 9.13 (1H, d), 7.54 (1H, dd), 7.38 (1H, d), 7.31 (2H, d), 7.23 (1H, d), 7.05 (2H, d), 6.75 (1H, d), 3.94 (3H, s), 2.37 (3H, s), 1.45 (18H, s).

Intermediate 7

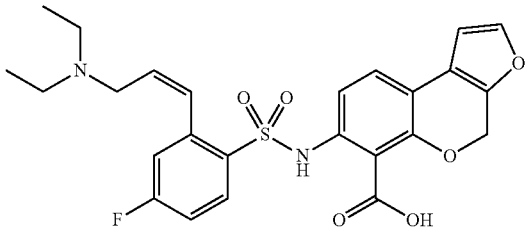
Methyl
6-amino-3-(2-formylfuran-3-yl)-2-hydroxybenzoate



A mixture of methyl 6-amino-3-bromo-2-hydroxybenzoate (prepared according to Wang et al, *Bioorg Med Chem Lett,* 2007, 17, 2817; 1.84 g), 2-formylfuran-3-boronic acid pinacol ester (1.99 g), tri-tert-butylphosphonium tetrafluoroborate (0.218 g), cesium carbonate (7.33 g) and tris-(dibenzylideneacetone)dipalladium (0.343 g) in dioxane (75 mL) and water (9.4 mL) was heated at 65° C., under nitrogen, for 1 hour. After cooling, the mixture was diluted with ethyl acetate and water and the organic layer was separated, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 10-50% to give methyl 6-amino-3-(2-formylfuran-3-yl)-2-hydroxybenzoate (1.72 g) as a yellow solid. The material was used without further characterisation.

Intermediate 8

7-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-4H-furo[2,3-c]chromene-6-carboxylic acid



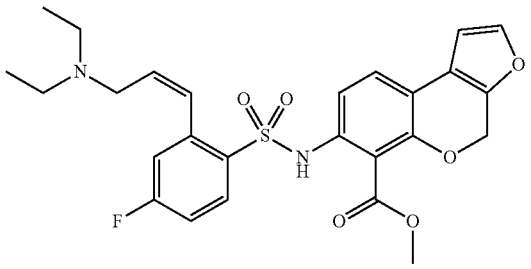
Methyl 7-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-4H-furo[2,3-c]chromene-6-carboxylate (Intermediate 9, 0.129 g) was added to a solution of lithium hydroxide monohydrate (0.42 g) in water (2 mL) and dioxane (8 mL), and the mixture was irradiated in the microwave at 130° C. for 1 hour. After cooling, the mixture was acidified with formic acid, and evaporated to dryness. The residue was triturated with 10% methanol in DCM, filtered and the filtrate was evaporated to dryness. The residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-10%. The isolated product was triturated with ethyl acetate and the solid was collected by filtration and dried in vacuo to give 7-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-4H-furo[2,3-c]chromene-6-carboxylic acid (0.056 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.71 (1H, d), 7.68 (1H, d), 7.38 (1H, d), 7.28 (1H, dd), 7.26-7.19 (2H, m), 7.02 (1H, d), 6.86 (1H, d), 6.20-6.11 (1H, m), 5.28 (2H, s), 3.79 (2H, d), 3.12 (4H, q), 1.14 (6H, t).

LCMS (Method C) r/t 3.48 (M+H) 501.

Intermediate 9

Methyl 7-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-4H-furo[2,3-c]chromene-6-carboxylate



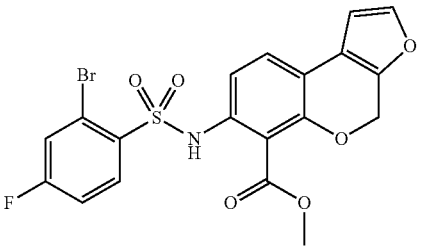
A mixture of methyl 7-(2-bromo-4-fluorobenzenesulfonylamino)-4H-furo[2,3-c]chromene-6-carboxylate (Intermediate 10, 2.04 g), N,N-diethyl-N—((Z)-1-tributylstannanyl-prop-1-en-3-yl)amine (Intermediate 11, 3.4 g), tri-tert-butylphosphonium tetrafluoroborate (0.246 g), tris-(dibenzylideneacetone)dipalladium (0.0.388 g) in dioxane (35 mL) was degassed and purged with argon then heated at 100° C. for 3.5 hours. After cooling, the mixture was diluted with ethyl acetate and filtered. The filtrate was washed with

water, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ammonia in methanol (2M) and DCM with a gradient of 0-10%. The product was triturated with ether and the solid was collected by filtration to give methyl 7-[2-((Z)-3-diethylaminoprop-1-en-1-yl)-4-fluorobenzenesulfonyl-amino]-4H-furo[2,3-c] chromene-6-carboxylate (1.47 g) as a pale orange solid.

^{1}H NMR ($CDCl_3$) δ: 8.06 (1H, dd), 7.40 (1H, m), 7.17 (1H, d), 7.14-6.98 (2H, m), 7.0-6.9 (2H, m), 6.56 (1H, d), 6.06 (1H, m), 5.37 (2H, s), 3.87 (3H, s), 3.17 (2H, m), 2.55 (4H, m), 0.97 (6H, t).

Intermediate 10

Methyl 7-(2-bromo-4-fluorobenzenesulfonylamino)-4H-furo[2,3-c]chromene-6-carboxylate

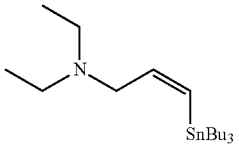


Methyl 7-[bis-(tert-butoxycarbonyl)amino]-4H-furo[2,3-c]-chromene-6-carboxylate (Intermediate 3, 2.66 g) was dissolved in formic acid (50 mL) and the mixture was stirred at room temperature for 90 minutes. The mixture was evaporated to dryness and the crude residue was partitioned between ethyl acetate and aqueous potassium carbonate solution (10%). The organic layer was separated, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was dissolved in DCM (20 mL) and pyridine (10 mL) and 2-bromo-4-fluorobenzenesulfonyl chloride (1.95 g) was added. The resultant mixture was stirred for 3.5 hours then evaporated to dryness. The residue was dissolved in DCM washed with water and filtered through a phase separator. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-60% to give methyl 7-(2-bromo-4-fluorobenzenesulfonyl-amino)-4H-furo[2,3-c]chromene-6-carboxylate (0.47 g) as a pale yellow solid.

^{1}H NMR ($CDCl_3$) δ: 9.25 (1H, br s), 8.14 (1H, dd), 7.40 (2H, m), 7.16 (2H, m), 7.12 (1H, m), 6.55 (1H, d), 5.36 (2H, s), 3.92 (3H, s).

Intermediate 11

N,N-Diethyl-N—((Z)-1-tributylstannanylprop-1-en-3-yl)-amine

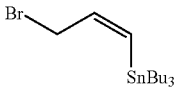


Diethylamine (19 mL) was added to a solution of ((Z)-3-bromoprop-1-enyl)-tributyl-stannane (Intermediate 12, 7.52 g) in THF (60 mL) and the mixture was stirred for 3 hours. The reaction mixture was evaporated to dryness and the residue was purified by chromatography on a silica column which had been pre-washed with 20% triethylamine in acetonitrile. The column was eluted with a mixture of ethyl acetate and pentane with a gradient of 0-10% to give N,N-diethyl-N—((Z)-1-tributylstannanylprop-1-en-3-yl)amine (4.75 g) as an orange oil.

^{1}H NMR ($CDCl_3$) δ: 6.59 (1H, dt), 5.97 (1H, dt), 3.08 (2H, dd), 2.53 (4H, q), 1.49 (6H, m), 1.37-1.24 (6H, m), 1.04 (6H, t), 0.92-0.89 (15H, m).

Intermediate 12

((Z)-3-Bromoprop-1-enyl)-tributylstannane

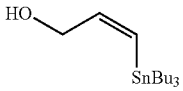


A solution of triphenylphosphine (5.32 g) in DCM (60 mL) was added to a solution of (Z)-3-tributylstannanylprop-2-en-1-ol (Intermediate 13, 6.4 g) and carbon tetrabromide (9.18 g) in DCM (60 mL) and the mixture was stirred for 2.5 hours. The mixture was evaporated to low volume and pentane was added. The solids were removed by filtration and the filtrate was evaporated to dryness. Pentane was added and the solids were again removed by filtration and the filtrate was evaporated to dryness to give ((Z)-3-bromoprop-1-enyl)-tributyl-stannane (12.14 g) as an oil.

^{1}H NMR ($CDCl_3$) δ: 6.71 (1H, dt), 6.11 (1H, d), 3.88 (2H, d), 1.52-1.50 (6H, m), 1.37-1.27 (6H, m), 0.99-0.97 (6H, m), 0.90 (9H, t).

Intermediate 13

(Z)-3=Tributylstannanylprop-2-en-1-ol

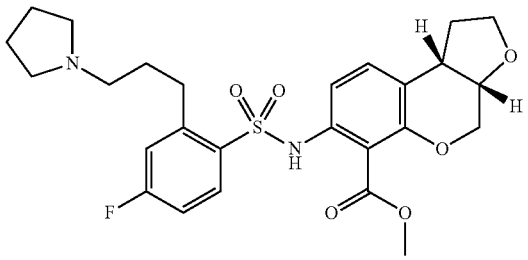


Propargyl alcohol (5 mL) was added to a solution of lithium aluminium hydride (1M in THF, 43 mL) in THF (70 mL) at −78° C. The resultant mixture was warmed to room temperature and stirred for 18 hours. It was re-cooled to −78° C. and a solution of tri-n-butyl tin chloride (8.32 mL) in diethyl ether (50 mL) was added and the mixture was stirred for 3 hours whilst gradually warming to room temperature. The reaction mixture was cooled to −5° C. and quenched by addition of water and 15% aqueous sodium hydroxide solution then warmed to room temperature. Ethyl acetate was added and the mixture was stirred for 1 hour. The mixture was filtered through Celite and the filtrate was evaporated to dryness. The residue was purified by chromatography on a silica column which had been pre-washed with 20% triethylamine in acetonitrile. The column was eluted with a mixture of ethyl acetate and pentane with a gradient of 0-10% to give (Z)-3-tributylstannanyl-prop-2-en-1-ol (5.06 g) as a clear oil.

^{1}H NMR ($CDCl_3$) δ: 6.70 (1H, dt), 6.08 (1H, dt), 4.12 (2H, dd), 1.49 (6H, m), 1.31 (6H, m), 0.98-0.84 (15H, m).

Intermediate 14

Methyl cis-(3aRS,9bRS)-7-[2-(3-{pyrrolidin-1-yl}propyl)-4-fluorobenzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate

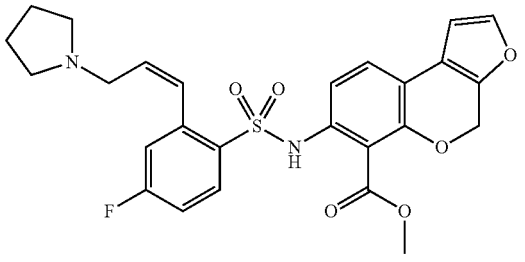


Mixture of cis enantiomers

A solution of methyl 7-[2-((Z)-3-{pyrrolidin-1-yl}prop-1-enyl)-4-fluorobenzene-sulfonylamino]-4H-furo[2,3-c] chromene-6-carboxylate (Intermediate 15, 0.06 g) in IMS (4 mL) and formic acid (2 drops) was treated under an atmosphere of nitrogen with palladium hydroxide on carbon (10%, 0.02 g). The nitrogen was replaced by hydrogen and the mixture was stirred under an atmosphere of hydrogen for 1 hour. The mixture was filtered through Celite and the filtrate was evaporated to dryness to give methyl cis-(3aRS,9bRS)-7-[2-(3-{pyrrolidin-1-yl}propyl)-4-fluorobenzene-sulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (0.06 g) which was used without further characterisation.

Intermediate 15

Methyl 7-[2-((Z)-3-{pyrrolidin-1-yl}prop-1-enyl)-4-fluorobenzene-sulfonylamino]-4H-furo[2,3-c] chromene-6-carboxylate

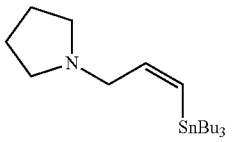


Prepared by proceeding in a similar manner to Intermediate 9, starting from methyl 7-(2-bromo-4-fluorobenzene-sulfonylamino)-4H-furo[2,3-c]chromene-6-carboxylate (Intermediate 10) and 1-((Z)-3-tributylstannanylallyl) pyrrolidine (Intermediate 16).

^{1}H NMR (CD_3OD) δ: 8.02 (1H, dd), 7.51 (1H, m), 7.16 (2H, d), 7.11-7.01 (2H, m), 6.76 (1H, d), 6.69 (1H, d), 5.93-5.83 (1H, m), 5.31 (2H, s), 3.80 (3H, s), 3.37-3.33 (2H, m), 2.69 (4H, m), 1.78 (4H, m).

Intermediate 16

1-((Z)-3-tributylstannanylallyl)pyrrolidine

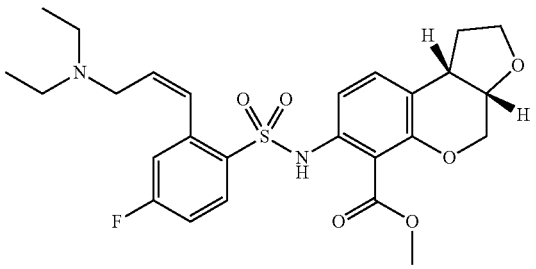


Prepared by proceeding in a similar manner to Intermediate 11 starting from ((Z)-3-bromoprop-1-enyl)tributylstannane (Intermediate 12) and pyrrolidine.

^{1}H NMR ($CDCl_3$) δ: 6.64 (1H, dt), 5.96 (1H, dt), 3.10 (2H, dd), 2.51 (4H, m), 1.79-1.78 (4H, m), 1.54-1.45 (6H, m), 1.36-1.26 (6H, m), 0.91-0.88 (15H, t).

Intermediate 17

Methyl cis-(3aRS,9bRS)-7-[2-((Z)-3-diethylamino-prop-1-enyl)-4-fluorobenzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate



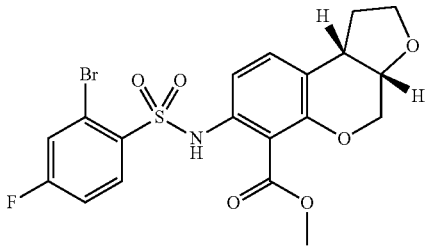
Mixture of cis enantiomers

Prepared by proceeding in a similar manner to Intermediate 9, starting from methyl cis-(3aRS,9bRS)-7-(2-bromo-4-fluorobenzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo [2,3-c]chromene-6-carboxylate (Intermediate 18) and N,N-diethyl-N—((Z)-1-tributylstannanylprop-1-en-3-yl)-amine (Intermediate 11) and heating at 80° C. for 2 hours.

LCMS (Method A) r/t 2.25 (M+H) 519.

Intermediate 18

Methyl cis-(3aRS,9bRS)-7-(2-bromo-4-fluorobenze-nesulfonyl-amino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate



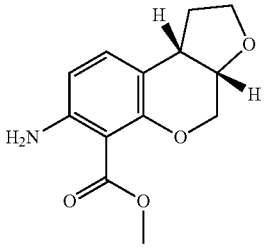
Mixture of cis enantiomers

2-Bromo-4-fluorobenzenesulfonyl chloride (0.335 g) was added to a solution of methyl cis-(3aRS,9bRS)-7-amino-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (Intermediate 19, 0.255 g) in DCM (4 mL) and pyridine (2 mL) and the resultant mixture was stirred at room temperature overnight. The mixture was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-100% to give methyl cis-(3aRS,9bRS)-7-(2-bromo-4-fluorobenzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (0.486 g) as a yellow gum.

^{1}H NMR ($CDCl_3$) δ: 9.47 (1H, s), 8.17 (1H, m), 7.42 (1H, dd), 7.12 (1H, dt), 7.11 (2H, s), 4.28 (1H, m), 4.06 (1H, dd), 3.96 (1H, dd), 3.91 (3H, s), 3.82 (2H, m), 3.41 (1H, m), 2.45 (1H, m), 1.84 (1H, m).

Intermediate 19

Methyl cis-(3aRS,9bRS)-7-amino-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate



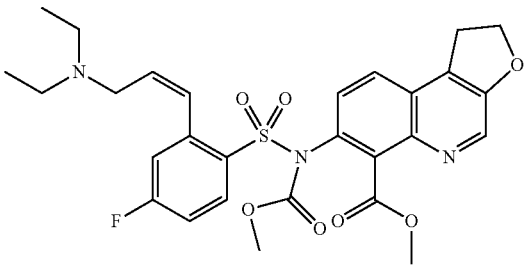
Mixture of cis enantiomers

Trifluoroacetic acid (7 mL) was added to a solution of methyl cis-(3aRS,9bRS)-7-[bis-(tert-butoxycarbonyl) amino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (Intermediate 2, 0.66 g) in DCM (15 mL) and the mixture was stirred at room temperature for 1 hour. The mixture was evaporated to dryness and the residue was treated with aqueous sodium bicarbonate and extracted with DCM, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give methyl cis-(3aRS,9bRS)-7-amino-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (0.255 g) as a gum.

^{1}H NMR ($CDCl_3$) δ: 7.0 (1H, dd), 6.31 (1H, d), 4.32 (1H, m), 4.01 (2H, m), 3.88 (3H, s), 3.84 (2H, m), 3.39 (1H, m), 2.41 (1H, m), 1.86 (1H, m).

Intermediate 20

Methyl 7-[N-{2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluoro-benzenesulfonyl}-N-(methoxycarbonyl) amino]-1,2-dihydrofuro[2,3-c]quinoline-6-carboxylate

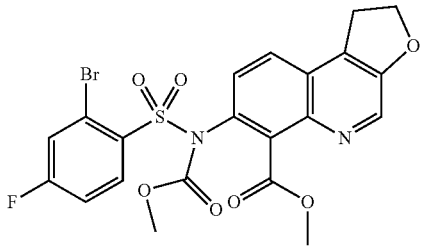


Prepared by proceeding in a similar manner to Intermediate 9, starting from methyl 7-[N-(2-bromo-4-fluorobenzenesulfonyl)-N-(methoxycarbonyl)amino]-1,2-dihydro-furo[2,3-c]quinoline-6-carboxylate (Intermediate 21) and N,N-diethyl-N—((Z)-1-tributylstannanylprop-1-en-3-yl)amine (Intermediate 11) and heating at 60° C. for 1 hour.

^{1}H NMR ($CDCl_3$) δ: 8.72 (1H, s), 8.32 (1H, dd), 7.76 (1H, d), 7.62 (1H, d), 7.22-7.08 (3H, m), 6.03 (1H, m), 4.87 (2H, t), 3.93 (3H, s), 3.62 (3H, s), 3.56 (2H, t), 3.20 (2H, m), 2.52 (4H, m), 0.97 (6H, t).

Intermediate 21

Methyl 7-[N-(2-bromo-4-fluorobenzenesulfonyl)-N-(methoxy-carbonyl)amino]-1,2-dihydrofuro[2,3-c] quinoline-6-carboxylate

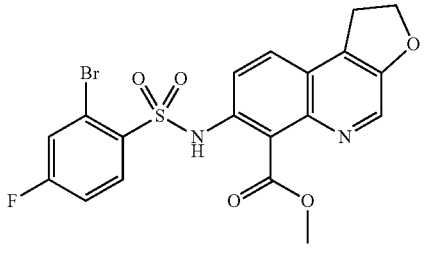


A solution of methyl 7-(2-bromo-4-fluorobenzenesulfonylamino)-1,2-dihydro-furo[2,3-c]quinoline-6-carboxylate (Intermediate 22, 0.29 g) in THF (5 mL) was added slowly to a suspension of sodium hydride (40% oil dispersion, 0.048 g) in THF (15 mL). Once the evolution of hydrogen had ceased, methyl chloroformate (0.147 g) was added and the mixture was stirred at room temperature for 1 hour. The mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was triturated with a mixture of ether and cyclohexane (1:1) and the solid was collected by filtration to give methyl 7-[N-(2-bromo-4-fluorobenzenesulfonyl)-N-(methoxy-carbonyl)amino]-1,2-dihydrofuro[2,3-c]quinoline-6-carboxylate (0.3 g) as a pale orange solid.

^{1}H NMR ($CDCl_3$) δ: 8.73 (1H, s), 8.48 (1H, dd), 7.76 (2H, s), 7.51 (1H, dd), 7.25 (1H, m), 4.86 (2H, t), 4.01 (3H, s), 3.66 (3H, s), 3.56 (2H, t).

Intermediate 22

Methyl 7-(2-bromo-4-fluorobenzenesulfonylamino)-1,2-dihydro-furo[2,3-c]quinoline-6-carboxylate



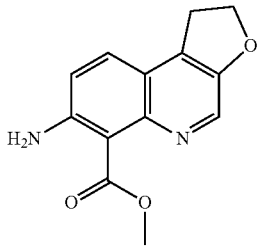
Prepared by proceeding in a similar manner to Intermediate 18, starting from methyl 7-amino-1,2-dihydrofuro[2,3-c]

quinoline-6-carboxylate (Intermediate 23) and 2-bromo-4-fluorobenzenesulfonyl chloride and stirring at room temperature for 3 days.

^{1}H NMR ($CDCl_3$) δ: 8.60 (1H, s), 8.07 (1H, dd), 7.84 (1H, d), 7.62 (1H, d), 7.43 (1H, dd), 7.06 (1H, m), 4.79 (2H, t), 4.02 (3H, s), 3.48 (2H, t).

Intermediate 23

Methyl 7-amino-12-dihydrofuro[2,3-c]quinoline-6-carboxylate

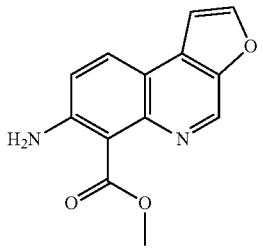


A solution of methyl 7-aminofuro[2,3-c]quinoline-6-carboxylate (Intermediate 24, 1.13 g) in a mixture of dioxane (5 mL) and acetic acid (5 mL) was treated under an atmosphere of nitrogen with palladium hydroxide on carbon (10%, 0.1 g). The nitrogen was replaced by hydrogen and the mixture was stirred under an atmosphere of hydrogen for 24 hours. The mixture was diluted with ethyl acetate and filtered through Celite and the filtrate was washed with 1M aqueous sodium hydroxide solution, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of methanol and ethyl acetate with a gradient of 0-10%. The isolated product was triturated with a mixture of ether and cyclohexane and the solid was collected by filtration to give methyl 7-amino-1,2-dihydrofuro[2,3-c]quinoline-6-carboxylate (0.666 g) as a yellow solid.

^{1}H NMR ($CDCl_3$) δ: 8.56 (1H, s), 7.51 (1H, d), 6.95 (1H, d), 5.16 (2H, br s), 4.74 (2H, t), 4.05 (3H, s), 3.46 (2H, t).

Intermediate 24

Methyl 7-aminofuro[2,3-c]quinoline-6-carboxylate

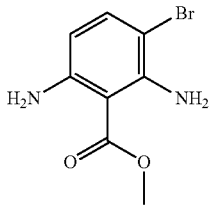


A mixture of methyl 3-bromo-2,6-diaminobenzoate (Intermediate 25, 1.34 g), 2-formylfuran-3-boronic acid pinacol ester (1.46 g), tri-tert-butylphosphonium tetrafluoroborate (0.305 g), cesium carbonate (5.15 g) and tris-(dibenzylideneacetone)dipalladium (0.49 g) in a mixture of dioxane (80 mL) and water (30 mL) was degassed and purged with argon then heated at 60° C. for 1 hour. After cooling, the mixture was filtered through Celite and the pad was washed thoroughly with ethyl acetate. The filtrate was washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-100% to give methyl 7-aminofuro[2,3-c]quinoline-6-carboxylate (1.13 g) as a brown gum.

^{1}H NMR ($CDCl_3$) δ: 9.11 (1H, s), 7.95 (1H, d), 7.82 (1H, d), 7.14 (1H, dd), 7.05 (1H, d), 5.05 (2H, br s), 4.08 (3H, s).

Intermediate 25

Methyl 3-bromo-2,6-diaminobenzoate

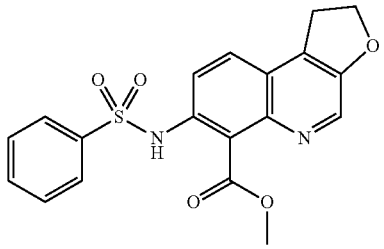


Iron powder (4.07 g) was added slowly with stirring and cooling to a solution of methyl 6-amino-3-bromo-2-nitrobenzoate (prepared according to Brock et al, Tetrahedron, 1963, 19, 1911; 2.0 g) in a mixture of absolute ethanol (49 mL), acetic acid (5 mL), formic acid (0.7 mL) and water (15 mL). On completion of the addition, the mixture was stirred at room temperature for 2 hours. The mixture was diluted with DCM and water (1:1) then filtered through Celite. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with 1M aqueous sodium hydroxide solution, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was triturated with ether and cyclohexane (1:1) and the solid was collected by filtration to give methyl 3-bromo-2,6-diaminobenzoate (1.34 g) as a pale yellow solid.

^{1}H NMR ($CDCl_3$) δ: 7.21 (1H, d), 6.11 (2H, br s), 5.88 (1H, d), 5.46 (2H, br s), 3.93 (3H, s).

Intermediate 26

Methyl 7-(benzenesulfonylamino)-1,2-dihydro[furo[2,3-c]quinoline-6-carboxylate

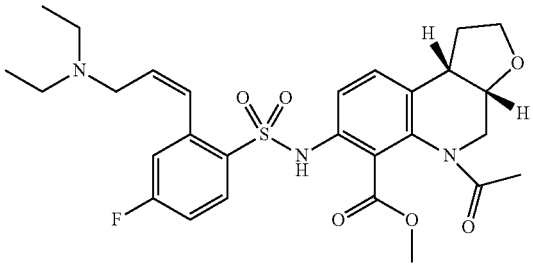


Prepared by proceeding in a similar manner to Intermediate 18, starting from methyl 7-amino-1,2-dihydrofuro[2,3-c]quinoline-6-carboxylate (Intermediate 23) and benzenesulfonyl chloride and stirring at room temperature overnight.

^{1}H NMR ($CDCl_3$) δ: 8.59 (1H, s), 7.94 (1H, d), 7.70 (1H, d), 7.50 (1H, m), 7.40 (2H, t), 7.21 (2H, m), 4.81 (2H, t), 3.75 (3H, s), 3.51 (2H, t).

Intermediate 27

Methyl cis-(3aRS,9bRS)-5-acetyl-7-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-6-carboxylate



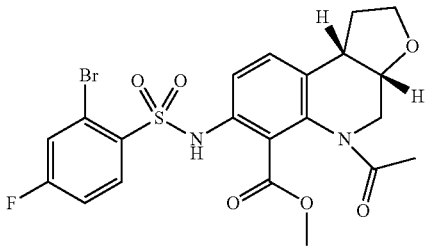
Mixture of cis enantiomers

Prepared by proceeding in a similar manner to Intermediate 9, starting from methyl cis-(3aRS,9bRS)-5-acetyl-7-(2-bromo-4-fluorobenzenesulfonylamino)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-6-carboxylate (Intermediate 28) and heating at 80° C. for 2 hours.

LCMS (Method B) r/t 2.29 (M+H) 560.

Intermediate 28

Methyl cis-(3aRS,9bRS)-5-acetyl-7-(2-bromo-4-fluorobenzene-sulfonylamino)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-6-carboxylate



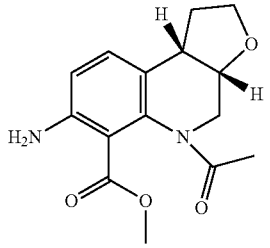
Mixture of cis enantiomers

Prepared by proceeding in a similar manner to Intermediate 18, starting from methyl cis-(3aRS,9bRS)-5-acetyl-7-amino-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-6-carboxylate (Intermediate 29) and 2-bromo-4-fluorobenzenesulfonyl chloride.

^{1}H NMR ($CDCl_3$) δ: 9.51 (1H, br s), 8.16 (1H, m), 7.42 (1H, dd), 7.34 (1H, d), 7.18 (1H, d), 7.12 (1H, dt), 4.46 (1H, d), 3.84 (2H, m), 3.81 (3H, s), 3.67 (1H, m), 3.49 (1H, m), 3.38-3.19 (1H, m), 2.41-2.30 (1H, m), 2.25 (3H, s), 1.57 (1H, m).

Intermediate 29

Methyl cis-(3aRS,9bRS)-5-acetyl-7-amino-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-6-carboxylate



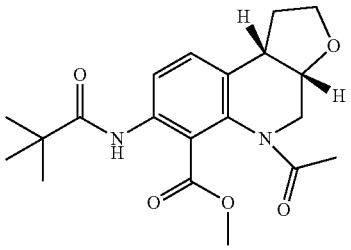
Mixture of cis enantiomers

Concentrated sulfuric acid (5 drops) was added to a solution of methyl cis-(3aRS,9bRS)-5-acetyl-7-(2,2-dimethylpropionylamino)-1,2,3a,4,5,9b-hexahydro-furo[2,3-c]quinoline-6-carboxylate (Intermediate 30, 0.15 g) in methanol (5 mL) and the solution was stirred and heated at reflux for 48 hours. After cooling, the mixture was evaporated to low volume and the residue was dissolved in ethyl acetate and carefully washed with saturated aqueous sodium bicarbonate solution. The organic layer was filtered through a phase separator and the filtrate was evaporated to dryness to give methyl cis-(3aRS,9bRS)-5-acetyl-7-amino-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-6-carboxylate (0.09 g) as a brown gum.

^{1}H NMR ($CDCl_3$) δ: 7.04 (1H, d), 6.53 (1H, d), 4.97 (2H, br s), 4.47 (1H, m), 3.90 (2H, m), 3.79 (3H, s), 3.67 (1H, m), 3.45 (1H, m), 3.30 (1H, m), 2.4-2.32 (1H, m), 2.27 (3H, s), 1.68-1.54 (1H, m).

Intermediate 30

Methyl cis-(3aRS,9bRS)-5-acetyl-7-(2,2-dimethylpropionylamino)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-6-carboxylate



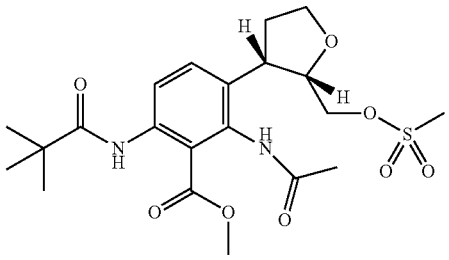
Mixture of cis enantiomers

Sodium hydride (60% oil dispersion, 0.02 g) was added to a solution of methyl 2-acetylamino-6-(2,2-dimethylpropionylamino)-3-[cis-(2RS,3RS)-2-(methanesulfonyl-oxymethyl)tetrahydrofuran-3-yl]benzoate (Intermediate 31, 0.166 g) in THF (3 mL) and the mixture was stirred at room temperature for 20 minutes. A saturated aqueous solution of ammonium chloride was added and the mixture was extracted with DCM, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give methyl cis-(3aRS,9bRS)-5-acetyl-7-(2,2-dimethylpropionylamino)-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-6-carboxylate (0.15 g) as a tan coloured solid.

^{1}H NMR ($CDCl_3$) δ: 9.92 (1H, s), 8.29 (1H, d), 7.30 (1H, d), 4.51 (1H, d), 3.82 (3H, s), 3.75 (2H, m), 3.69 (1H, m), 3.56 (1H, m), 3.37-3.27 (1H, br m), 2.44-2.34 (1H, br m), 2.29 (3H, s), 1.68-1.58 (1H, br m), 1.29 (9H, s).

Intermediate 31

Methyl 2-acetylamino-6-(2,2-dimethylpropionylamino)-3-[cis-(2RS,3RS)-2-(methanesulfonyloxymethyl)tetrahydrofuran-3-yl]benzoate



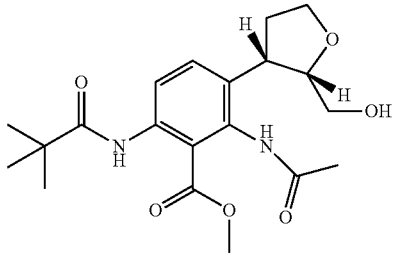
Mixture of cis enantiomers

Methanesulfonyl chloride (0.042 mL) was added to a mixture of methyl 2-acetylamino-6-(2,2-dimethylpropionylamino)-3-[cis-(2RS,3RS)-2-(hydroxymethyl)-tetrahydrofuran-3-yl]benzoate (Intermediate 32, 0.14 g) and triethylamine (0.15 mL) in DCM (5 mL) and the resultant mixture was stirred at room temperature for 30 minutes. The mixture was washed with 1M hydrochloric acid, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give methyl 2-acetylamino-6-(2,2-dimethylpropionylamino)-3-[cis-(2RS,3RS)-2-(methanesulfonyloxymethyl)-tetrahydrofuran-3-yl]benzoate (0.166 g) as a gum.

LCMS (Method B) r/t 2.57 (M+Na) 493.

Intermediate 32

Methyl 2-acetylamino-6-(2,2-dimethylpropionylamino)-3-[cis-(2RS,3RS)-2-(hydroxymethyl)-tetrahydrofuran-3-yl]benzoate



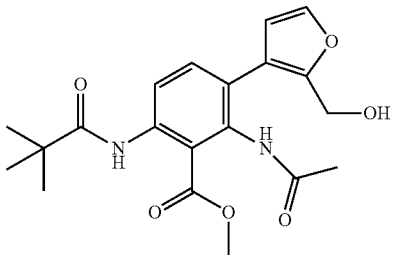
Mixture of cis enantiomers

A solution of methyl 2-acetylamino-6-(2,2-dimethylpropionylamino)-3-(2-hydroxymethylfuran-3-yl)benzoate (Intermediate 38, 0.2 g) in dioxane (4 mL) and acetic acid (1 mL) was treated under an atmosphere of nitrogen with palladium hydroxide on carbon (10%, 0.03 g). The nitrogen was replaced by hydrogen and the mixture was stirred under an atmosphere of hydrogen overnight. The mixture was filtered through Celite and the pad was washed thoroughly with ethyl acetate. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of methanol and ethyl acetate with a gradient of 0-10% to give methyl 2-acetylamino-6-(2,2-dimethylpropionylamino)-3-[cis-(2RS,3RS)-2-(hydroxymethyl)tetrahydrofuran-3-yl]benzoate (0.14 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 9.70 (1H, br s), 8.29 (1H, d), 8.25 (1H, br s), 7.36 (1H, d), 4.22 (1H, m), 4.10 (1H, m), 3.91 (1H, m), 3.90 (3H, s), 3.64 (2H, m), 3.24 (1H, m), 2.41 (1H, m), 2.16 (3H, s), 2.11 (1H, m), 1.30 (9H, s).

Intermediate 33

Methyl 2-acetylamino-6-(2,2-dimethylpropionylamino)-3-(2-hydroxymethylfuran-3-yl)benzoate

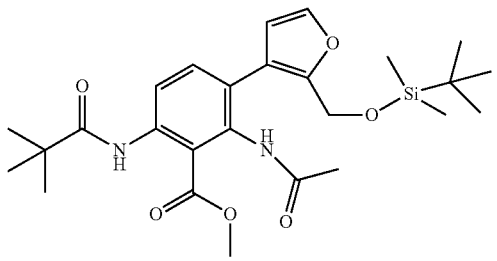


Tetrabutylammonium fluoride (1M solution in THF, 1.1 mL) was added to a stirred, cooled solution of methyl 2-acetylamino-3-[2-(tert-butyldimethylsilanyloxymethyl)-furan-3-yl]-6-(2,2-dimethylpropionylamino)benzoate (Intermediate 34, 0.43 g) in THF (10 mL) at 0° C. and the mixture was stirred at 0° C. for 40 minutes then evaporated to dryness. The residue was partitioned between ethyl acetate and water and the organic layer was washed with brine, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of methanol and ethyl acetate with a gradient of 0-2% to give methyl 2-acetylamino-6-(2,2-dimethylpropionylamino)-3-(2-hydroxymethylfuran-3-yl)benzoate (0.2 g) as a gum.

^{1}H NMR ($CDCl_3$) δ: 9.95 (1H, br s), 8.36 (1H, d), 8.00 (1H, br s), 7.46 (1H, s), 7.36 (1H, d), 6.32 (1H, s), 4.54 (2H, d), 3.90 (3H, s), 2.45 (1H, t), 1.99 (3H, s), 1.32 (9H, s).

Intermediate 34

Methyl 2-acetylamino-3-[2-(tert-butyldimethylsilanyloxymethyl)-furan-3-yl]-6-(2,2-dimethylpropionylamino)benzoate



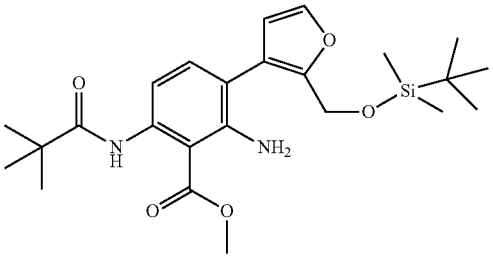
Acetyl chloride (0.09 mL) was added to a stirred solution of methyl 2-amino-3-[2-(tert-butyldimethylsilanyloxymethyl)furan-3-yl]-6-(2,2-dimethylpropionylamino)-benzoate (Intermediate 35, 0.47 g) in DCM (5 mL) and pyridine (0.16

mL) and the mixture was stirred at room temperature for 1 hour. The mixture was diluted with DCM and washed with water and brine, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 20-50% to give methyl 2-acetylamino-3-[2-(tert-butyldimethylsilanyloxymethyl)-furan-3-yl]-6-(2,2-dimethylpropionylamino)benzoate (0.442 g) as a colourless foam.

^{1}H NMR ($CDCl_3$) δ: 10.08 (1H, br s), 8.34 (1H, d), 8.15 (1H, br s), 7.46 (1H, s), 7.36 (1H, d), 6.32 (1H, s), 4.51 (2H, s), 3.93 (3H, s), 1.98 (3H, s), 1.32 (9H, s), 0.93 (9H, s), 0.13 (6H, s).

Intermediate 35

Methyl 2-amino-3-[2-(tert-butyldimethylsilanyloxymethyl)furan-3-yl]-6-(2,2-dimethylpropionylamino)-benzoate

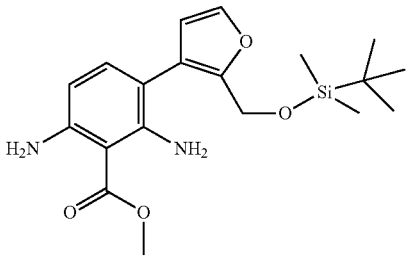


Pivaloyl chloride (0.353 g) was added to a stirred, cooled mixture of methyl 2,6-diamino-3-[2-(tert-butyldimethylsilanyloxymethyl)furan-3-yl]benzoate (Intermediate 36, 1.0 g) and sodium bicarbonate (0.268 g) in ethyl acetate (20 mL) and water (7 mL) at 0° C. The mixture was allowed to warm to room temperature and stirred for 1.5 hours. Further pivaloyl chloride (0.048 g) was added and the mixture was stirred for 1 hour. Ethyl acetate was added and the layers were separated. The organic layer was washed with aqueous sodium bicarbonate solution dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 5-20% to give methyl 2-amino-3-[2-(tert-butyldimethylsilanyloxymethyl) furan-3-yl]-6-(2,2-dimethylpropionylamino)benzoate (0.744 g) as an oil.

^{1}H NMR ($CDCl_3$) δ: 10.81 (1H, br s), 7.97 (1H, d), 7.48 (1H, s), 7.18 (1H, d), 6.41 (1H, s), 5.67 (2H, s), 4.51 (2H, s), 3.98 (3H, s), 1.33 (9H, s), 0.87 (9H, s), 0.05 (6H, s).

Intermediate 36

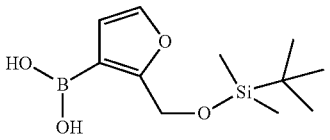
Methyl 2,6-diamino-3-[2-(tert-butyldimethylsilanyloxymethyl)-furan-3-yl]benzoate



A mixture of methyl 3-bromo-2,6-diaminobenzoate (Intermediate 25, 2.6 g), 2-(tert-butyldimethylsilanyloxymethyl) furan-3-boronic acid (Intermediate 37, 3.5 g), cesium carbonate (11.35 g), tri-tert-butylphosphonium tetrafluoroborate (0.334 g) and tris-(dibenzylideneacetone)dipalladium (0.529 g) in dioxane (72 mL) and water (18 mL) was degassed and purged with nitrogen then heated at 70° C. for 75 minutes. After cooling, ethyl acetate and water were added and the mixture was filtered through Celite. The filtrate was separated and the organic layer was washed with brine, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 5-20% to give methyl 2,6-diamino-3-[2-(tert-butyldimethylsilanyloxymethyl)furan-3-yl]benzoate (2.39 g) as a viscous oil which was used without further characterization.

Intermediate 37

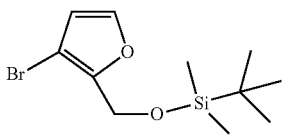
2-(tert-Butyldimethylsilanyloxymethyl)furan-3-boronic acid



n-Butyllithium (2.5M in hexanes, 11.25 mL) was added slowly to a stirred, cooled solution of 3-bromo-2-(tert-butyldimethylsilanyloxymethyl)furan (Intermediate 38, 7.5 g) in dry ether (150 mL) while maintaining the temperature below −70° C. The mixture was stirred at −78° C. for 2.5 hours. Tri-isopropyl borate (6.75 g) was added and the mixture was allowed to warm to room temperature and stirred for 1.75 hours. Ethyl acetate and aqueous ammonium chloride solution were added and the layers were separated. The organic layer was washed with aqueous ammonium chloride solution, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 10-35% to give 2-(tert-butyldimethylsilanyloxymethyl)furan-3-boronic acid (3.6 g) which was used directly without further characterization.

Intermediate 38

3-Bromo-2-(tert-butyldimethylsilanyloxymethyl) furan



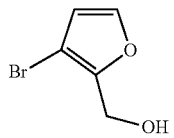
tert-Butyldimethylsilanyl triflate (17.13 g) was added slowly to a stirred, cooled solution of 3-bromo-2-hydroxymethylfuran (Intermediate 39, 10.1 g) in DCM (160 mL) and pyridine (9.57 g) while maintaining the temperature at 0° C. The mixture was allowed to warm to room temperature and stirred for 1 hour. The mixture was washed with aqueous

citric acid solution, brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give 3-bromo-2-(tert-butyldimethylsilanyloxymethyl)furan (17.1 g).

^{1}H NMR ($CDCl_3$) δ: 7.35 (1H, d), 6.38 (1H, d), 4.65 (2H, s), 0.90 (9H, s), 0.09 (6H, s).

Intermediate 39

3-Bromo-2-hydroxymethylfuran

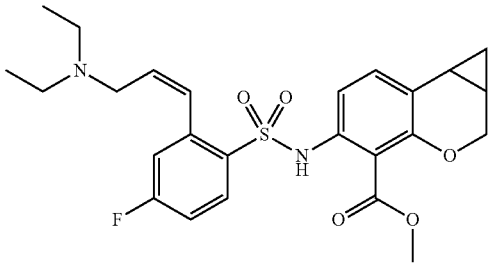


Sodium borohydride (1.14 g) was added slowly to a stirred, cooled solution of 3-bromo-2-formylfuran (5 g) in a mixture of THF (50 mL) and methanol (25 mL) while maintaining the temperature around 0° C. The mixture was allowed to warm to room temperature and stirred for 1 hour. The mixture was evaporated to dryness and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give 3-bromo-2-hydroxymethylfuran (5.31 g) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ: 7.37 (1H, d), 6.42 (1H, d), 4.65 (2H, d), 1.71 (1H, t).

Intermediate 40

Methyl (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

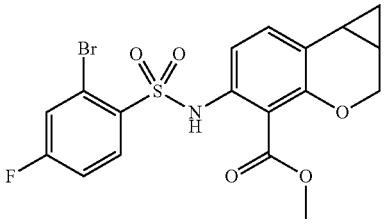


A solution of methyl (1aRS,7bSR)-5-(2-bromo-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 41, 0.208 g) and N,N-diethyl-N—((Z)-1-tributylstannanylprop-1-en-3-yl)-amine (Intermediate 11, 0.367 g) in dioxane (5 mL) and DMSO (0.5 mL) was de-gassed and flushed with nitrogen. Tris-(dibenzylideneacetone)-dipalladium (0.021 g) and tri-tert-butylphosphonium tetrafluoroborate (0.013 g) were added and the mixture was again de-gassed and flushed with nitrogen. The resultant mixture was heated at 95° C. for 45 minutes. After cooling, the mixture was partitioned between ethyl acetate and water and the organic layer was dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM, with a gradient of 0-12% to give methyl (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.188 g) as a yellow/brown oil.

^{1}H NMR ($CDCl_3$) δ: 8.06 (1H, dd), 7.16 (1H, d), 7.09-7.03 (2H, m), 6.94 (1H, d), 6.86 (1H, d), 6.10-6.02 (1H, m), 4.33 (1H, d), 3.84 (3H, s), 3.78 (1H, d), 3.13 (2H, br, d), 2.54 (4H, br, q), 1.88 (1H, m), 1.71 (1H, m), 1.03-0.92 (8H, m).

Intermediate 41

Methyl (1aRS,7bSR)-5-(2-bromo-4-fluorobenzene-sulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

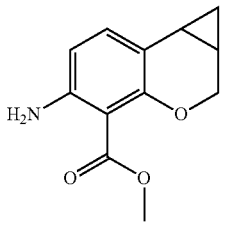


Methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 42, 0.120 g) was suspended in DCM (5 mL). Pyridine (0.885 mL) and 2-bromo-4-fluorobenzenesulfonyl chloride (0.180 g) were added. The mixture was stirred at room temperature for 5 hours then concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with 0.5M aqueous hydrochloric acid solution, dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane, with a gradient of 5-10% to give methyl (1aRS,7bSR)-5-(2-bromo-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.208 g) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ: 9.31 (1H, br, s), 8.14 (1H, dd), 7.41 (1H, dd), 7.17 (1H, d), 7.11 (1H, ddd), 7.06 (1H, d), 4.34 (1H, dd), 3.90 (3H, s), 3.80 (1H, dd), 1.94-1.85 (1H, m), 1.75-1.67 (1H, m), 1.01 (2H, m).

Intermediate 42

Methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate



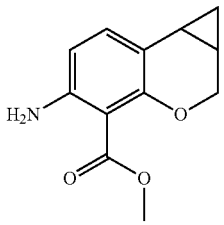
Methyl (1aRS,7bSR)-5-(2,2-dimethylpropionylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 43, 0.310 g) was suspended in methanol (7.5 mL) and concentrated sulphuric acid (4 drops) was added.

The reaction mixture was heated to reflux, under an atmosphere of nitrogen, for 36 hours. A further 2 drops of concentrated sulphuric acid was added and heating was continued for a further 24 hours. After cooling, the mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate and saturated aqueous potassium carbonate solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane, with a gradient of 5-20% to give methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.120 g) as an off-white solid.

^{1}H NMR ($CDCl_3$) δ: 7.06 (1H, d), 6.26 (1H, d), 4.33 (1H, d), 3.87 (3H, s), 3.85 (1H, d), 1.83 (1H, td), 1.64 (1H, m), 0.99-0.89 (2H, m).

Intermediate 42A

Methyl (1aR,7bS)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

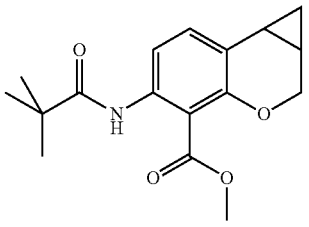


Sample from Intermediate 42 was subjected to chiral SFC separation using a Lux C_{1-3} column, 50 mm×250 mm, particle size 5 micron. Eluting with 5% methanol (+0.1% diethylamine) in CO_2

Absolute configuration of Intermediate 42A was confirmed by conversion of a sample to Example 12 and comparison with the analytical chiral HPLC.

Intermediate 43

Methyl (1aRS,7bSR)-5-(2,2-dimethylpropionylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

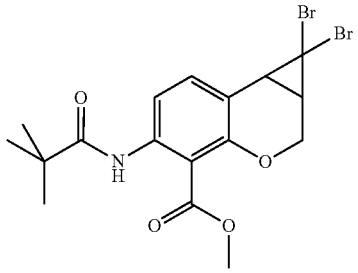


Methyl (1aRS,7bSR)-1,1-dibromo-5-(2,2-dimethylpropionylamino)-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (Intermediate 44, 1.13 g) was suspended in ethanol (30 mL). Zinc dust (1.17 g), followed by ammonium chloride (1.31 g) were added and the reaction mixture was heated to reflux, under an atmosphere of nitrogen, for 6 hours. After cooling, the solid was filtered off and washed with ethyl acetate. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ether and cyclohexane, with a gradient of 5-12.5% to give methyl (1aRS,7bSR)-5-(2,2-dimethylpropionylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.310 g) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ: 9.72 (1H, br, s), 7.98 (1H, d), 7.30 (1H, d), 4.36 (1H, dd), 3.91 (3H, s), 3.84 (1H, dd), 1.95 (1H, td), 1.73 (1H, m), 1.28 (9H, s), 1.03 (2H, m).

Intermediate 44

Methyl (1aRS,7bSR)-1,1-dibromo-5-(2,2-dimethylpropionylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

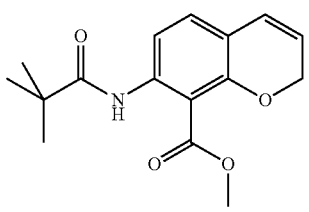


Methyl 7-(2,2-dimethylpropionylamino)-2H-chromene-8-carboxylate (Intermediate 45, 2.372 g) and benzyl triethyl ammonium chloride (0.373 g) were suspended in bromoform (6.45 mL) and aqueous sodium hydroxide solution (50%, 3.64 mL) was added dropwise. The resultant black suspension was heated to 60° C. for 2 hours. After cooling, the mixture was partitioned between water and ethyl acetate. The emulsion formed was filtered through a pad of Celite and the organic layer was decanted off. The aqueous was re-extracted with ethyl acetate and the combined organic layers were dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane, with a gradient of 2.5-15% to give methyl 1,1-dibromo-5-(2,2-dimethylpropionylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (1.557 g) as an off-white solid.

^{1}H NMR ($CDCl_3$) δ: 9.89 (1H, br, s), 8.13 (1H, d), 7.43 (1H, d), 4.47 (1H, dd), 4.32 (1H, dd), 3.91 (3H, s), 2.89 (1H, d), 2.45 (1H, ddd), 1.30 (9H, s).

Intermediate 45

Methyl 7-(2,2-dimethylpropionylamino)-2H-chromene-8-carboxylate

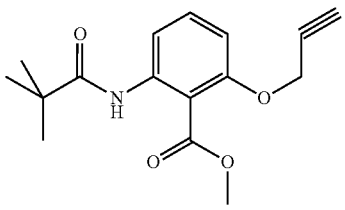


A solution of methyl 2-(2,2-dimethylpropionylamino)-6-(prop-2-ynyloxy)benzoate (Intermediate 46, 4.74 g) and [bis(trifluoromethanesulfonyl)imidate]-(triphenylphosphine) gold (2:1) toluene adduct (0.060 g) in toluene (70 mL) was heated to 85° C., under an atmosphere of nitrogen for 3 hours. After cooling, the mixture was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane, with a gradient of 0-20% to give methyl 7-(2,2-dimethylpropionylamino)-2H-chromene-8-carboxylate (3.59 g) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ: 10.02 (1H, br, s), 8.05 (1H, d), 7.05 (1H, d), 6.39 (1H, ddd), 5.76 (1H, dt), 4.83 (2H, dd), 3.93 (3H, s), 1.30 (9H, s).

Intermediate 46

Methyl 2-(2,2-dimethylpropionylamino)-6-(prop-2-ynyloxy)benzoate

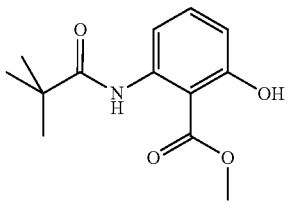


A mixture of methyl 2-(2,2-dimethylpropionylamino)-6-hydroxybenzoate (Intermediate 47, 4.57 g), propargyl bromide (80% solution in toluene, 2.03 mL) and potassium carbonate (3.74 g) in acetone (35 mL) was heated at reflux for 8 hours. After cooling, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane, with a gradient of 5-20% to give methyl 2-(2,2-dimethylpropionylamino)-6-(prop-2-ynyloxy)benzoate (4.74 g) as an oil which crystallised on standing to give a white solid.

^{1}H NMR ($CDCl_3$) δ: 9.89 (1H, br, s), 8.16 (1H, dd), 7.41 (1H, t), 6.83 (1H, dd), 4.74 (2H, d), 3.95 (3H, s), 2.53 (1H, t), 1.31 (9H, s).

Intermediate 47

Methyl 2-(2,2-dimethylpropionylamino)-6-hydroxybenzoate

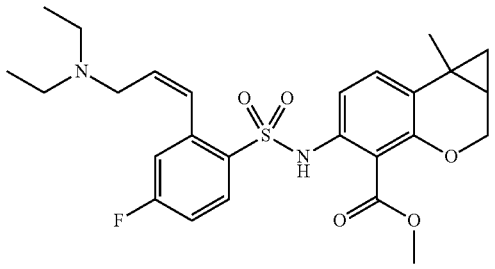


Trimethylacetyl chloride (3.69 g) was added to a mixture of methyl 2-amino-6-hydroxybenzoate (prepared according to Comess et al, US2004 0167128, 3.99 g) and sodium bicarbonate (2.57 g) in ethyl acetate (77 mL) and water (18 mL). The reaction mixture was stirred at room temperature for 1 hour. A further amount of trimethylacetyl chloride (1.85 g) was added and the mixture was stirred for 1 hour. A further amount of trimethylacetyl chloride (0.920 g) was added and the mixture was stirred for 30 minutes. The mixture was diluted with ethyl acetate, the layers were separated and the organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane, with a gradient of 5-25% to give methyl 2-(2,2-dimethylpropionylamino)-6-hydroxybenzoate (5.79 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 10.32 (1H, br, s), 8.22 (1H, dd), 7.41 (1H, t), 6.71 (1H, dd), 4.08 (3H, s), 1.33 (9H, s).

Intermediate 48

Methyl (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

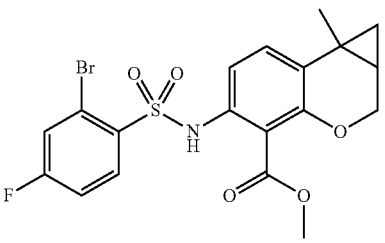


Prepared by proceeding in a similar manner to Intermediate 40, starting from methyl (1aRS,7bSR)-5-(2-bromo-4-fluorobenzenesulfonylamino)-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 49) and N,N-diethyl-N—((Z)-1-tributylstannanylprop-1-en-3-yl)amine (Intermediate 11).

^{1}H NMR ($CDCl_3$) δ: 8.07 (1H, dd), 7.28 (1H, d), 7.05 (2H, m), 6.95 (1H, d), 6.88 (1H, d), 6.06 (1H, m), 4.28 (1H, d), 3.85 (3H, s), 3.83 (1H, d), 3.14 (2H, br d), 2.53 (4H, q), 1.41 (3H, s), 1.12 (1H, m), 1.07 (1H, t), 0.93 (6H, t), 0.84 (1H, dd).

Intermediate 49

Methyl (1aRS,7bSR)-5-(2-bromo-4-fluorobenzenesulfonylamino)-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

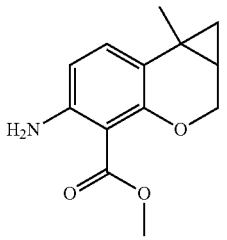


Prepared by proceeding in a similar manner to Intermediate 41, starting from methyl (1aRS,7bSR)-5-amino-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 50) and 2-bromo-4-fluorobenzenesulfonyl chloride.

^{1}H NMR ($CDCl_3$) δ: 9.18 (1H, br s), 8.14 (1H, dd), 7.41 (1H, dd), 7.29 (1H, d), 7.11 (1H, m), 7.08 (1H, d), 4.28 (1H, d), 3.89 (3H, s), 3.84 (1H, d), 1.44 (1H, m), 1.42 (3H, s), 1.10 (1H, t), 0.83 (1H, dd).

Intermediate 50

Methyl (1aRS,7bSR)-5-amino-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

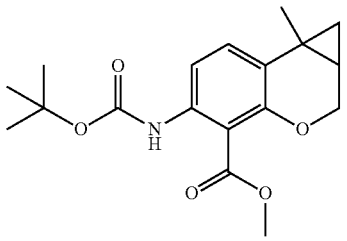


Trifluoroacetic acid (4 mL) was added to a solution of methyl (1aRS,7bSR)-5-(tert-butoxycarbonylamino)-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 51, 0.6 g) in dichloromethane (4 mL) and the resultant dark solution was stirred at room temperature for 1 hour. The solution was evaporated to dryness and the residue was partitioned between water and ethyl acetate and treated with a small amount of solid sodium bicarbonate until the pH of the aqueous layer was >7. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give methyl (1aRS,7bSR)-5-amino-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (0.402 g) as a red/orange solid.

^{1}H NMR ($CDCl_3$) δ: 7.20 (1H, d), 6.30 (1H, d), 4.27 (1H, d), 3.90 (1H, d), 3.88 (3H, s), 1.42 (3H, s), 1.37 (1H, m), 1.06 (1H, t), 0.78 (1H, dd).

Intermediate 51

Methyl (1aRS,7bSR)-5-(tert-butoxycarbonylamino)-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

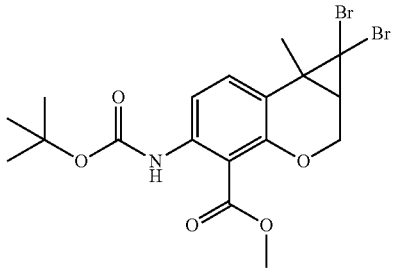


Prepared by proceeding in a similar manner to Intermediate 43, starting from methyl (1aRS,7bSR)-5-(tert-butoxycarbonylamino)-1,1-dibromo-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 52).

^{1}H NMR ($CDCl_3$) δ: 8.27 (1H, br s), 7.72 (1H, d), 7.38 (1H, d), 4.29 (1H, d), 3.91 (3H, s), 3.88 (1H, d), 1.50 (9H, s), 1.46 (3H, s), 1.44 (1H, m), 1.13 (1H, t), 0.84 (1H, dd).

Intermediate 52

Methyl (1aRS,7bSR)-1,1-dibromo-5-(tert-butoxycarbonylamino)-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

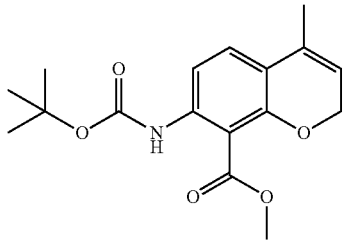


Prepared by proceeding in a similar manner to Intermediate 44, starting from methyl 4-methyl-7-(tert-butoxycarbonylamino)-2H-chromene-8-carboxylate (Intermediate 53).

^{1}H NMR ($CDCl_3$) δ: 8.55 (1H, br s), 7.87 (1H, d), 7.42 (1H, d), 4.75 (1H, dd), 4.13 (1H, dd), 3.92 (3H, s), 2.05 (1H, dd), 1.79 (3H, s), 1.50 (9H, s).

Intermediate 53

Methyl 4-methyl-7-(tert-butoxycarbonylamino)-2H-chromene-8-carboxylate

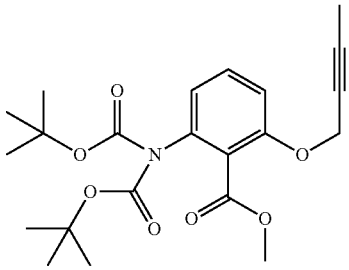


Prepared by proceeding in a similar manner to Intermediate 45, starting from methyl 2-[bis-(tert-butyoxycarbonyl)amino]-6-(but-2-ynyloxy)benzoate (Intermediate 54).

^{1}H NMR ($CDCl_3$) δ: 8.66 (1H, br s), 7.77 (1H, d), 7.18 (1H, dd), 5.53 (1H, m), 4.73 (2H, m), 3.93 (3H, s), 1.99 (3H, q), 1.51 (9H, s).

Intermediate 54

Methyl 2-[bis-(tert-butyoxycarbonyl)amino]-6-(but-2-ynyloxy)benzoate

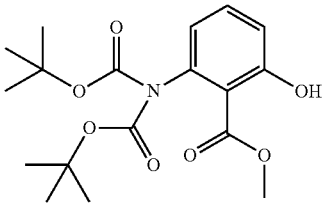


Prepared by proceeding in a similar manner to Intermediate 46, starting from methyl 2-[bis-(tert-butyoxycarbonyl) amino]-6-hydroxybenzoate (Intermediate 55) and 1-bromobut-2-yne

^{1}H NMR ($CDCl_3$) δ: 7.36 (1H, t), 7.08 (1H, dd), 6.82 (1H, dd), 4.70 (2H, q), 3.84 (3H, s), 1.84 (3H, t), 1.39 (18H, s).

Intermediate 55

Methyl 2-[bis-(tert-butyoxycarbonyl)amino]-6-hydroxybenzoate

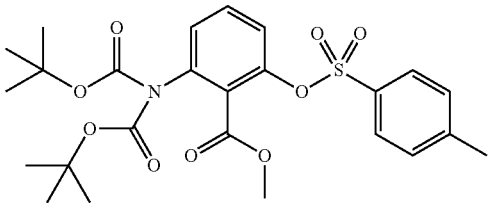


Prepared by proceeding in a similar manner to Intermediate 4, starting from methyl 2-[bis-(tert-butoxycarbonyl) amino]-6-(4-methylbenzenesulfonyloxy)benzoate (Intermediate 56)

^{1}H NMR ($CDCl_3$) δ: 11.17 (1H, s), 7.40 (1H, t), 6.99 (1H, dd), 6.69 (1H, dd), 3.92 (3H, s), 1.37 (18H, s).

Intermediate 56

Methyl 2-[bis-(tert-butoxycarbonyl)amino]-6-(4-methylbenzenesulfonyloxy)-benzoate

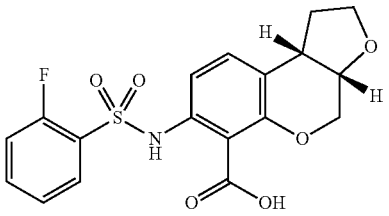


Prepared by proceeding in a similar manner to Intermediate 6, starting from methyl 2-amino-6-hydroxybenzoate (prepared according to Comess et al, US2004 0167128)

^{1}H NMR ($CDCl_3$) δ: 7.72 (2H, d), 7.40 (1H, t), 7.31 (2H, d), 7.22 (1H, dd), 7.11 (1H, dd), 3.71 (3H, s), 2.44 (3H, s), 1.33 (18H, s).

Intermediate 57

Cis-(3aRS,9bRS)-7-(2-fluorobenzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c] chromene-6-carboxylic acid



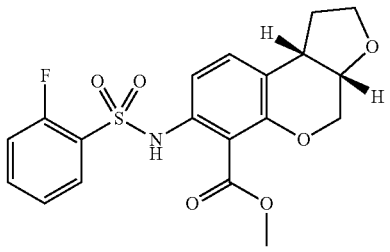
Mixture of cis enantiomers

A mixture of lithium hydroxide (0.5 g) and methyl cis-(3aRS,9bRS)-7-(2-fluorobenzenesulfonyl-amino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (Intermediate 58, 0.217 g) in a mixture of dioxane (13 mL) and water (4 mL) was divided between two microwave vials and the mixtures were irradiated in the microwave at 150° C. for 10 minutes. After cooling, the combined mixture was acidified by addition of 10% aqueous citric acid (2 mL), extracted with DCM, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give cis-(3aRS,9bRS)-7-(2-fluorobenzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid (0.518 g) as a glass.

^{1}H NMR ($CDCl_3$) δ: 12.00 (1H, br s), 11.57 (1H, br s), 7.97 (1H, dt), 7.55 (1H, m), 7.43 (1H, d), 7.26 (2H, m), 7.15 (1H, t), 4.43 (1H, dd), 4.37 (1H, m), 4.14 (1H, dd), 3.83 (2H, m), 3.50 (1H, m), 2.50 (1H, m), 1.87 (1H, m).

Intermediate 58

Methyl cis-(3aRS,9bRS)-7-(2-fluorobenzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c] chromene-6-carboxylate



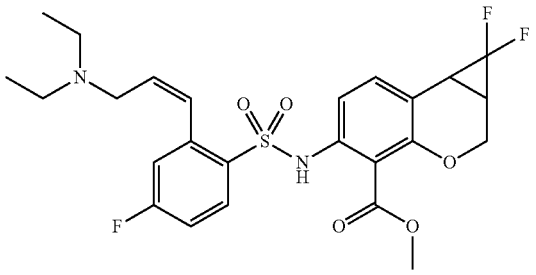
Mixture of cis enantiomers

2-Fluorobenzenesulfonyl chloride (0.5 g) was added to a solution of methyl cis-(3aRS,9bRS)-7-amino-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (Intermediate 19, 0.53 g) in DCM (10 mL) and pyridine (20 mL) and the resultant mixture was stirred at room temperature for 48 hours. The mixture was evaporated to dryness and the residue was treated with water, extracted with DCM, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-60% to give methyl cis-(3aRS,9bRS)-7-(2-fluorobenzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylate (0.574 g) as a pale yellow solid.

^{1}H NMR ($CDCl_3$) δ: 9.11 (1H, s), 7.85 (1H, dt), 7.53 (1H, m), 7.23 (1H, d), 7.21 (1H, dt), 7.15 (1H, d), 7.13 (1H, dd), 4.28 (1H, m), 4.04 (1H, dd), 3.95 (1H, dd), 3.87 (3H, s), 3.82 (2H, m), 3.41 (1H, m), 2.45 (1H, m), 1.84 (1H, m).

Intermediate 59

Methyl(1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1-difluoro-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate

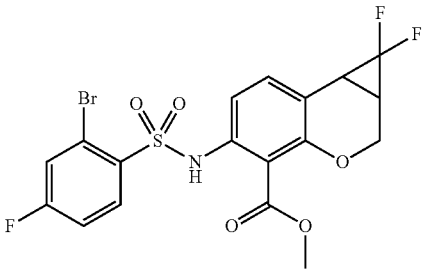


Prepared by proceeding in a similar manner to Intermediate 9, starting from methyl (1aRS,7bSR)-5-(2-bromo-4-fluorobenzenesulfonylamino)-1,1-difluoro-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (Intermediate 60) and N,N-diethyl-N—((Z)-1-tributylstannanylprop-1-en-3-yl)amine (Intermediate 11) as a pale yellow gum.

^{1}H NMR ($CDCl_3$) δ: 8.11 (1H, dd), 7.18 (1H, d), 7.13-7.04 (2H, m), 6.98 (1H, d), 6.93 (1H, d), 6.08 (1H, m), 4.38 (1H, d), 4.02 (1H, m), 3.87 (3H, s), 3.23-3.04 (2H, br s), 2.67 (1H, t), 2.60-2.43 (4H, br s), 3.32 (1H, m), 0.94 (6H, t).

Intermediate 60

Methyl (1aRS,7bSR)-5-(2-bromo-4-fluorobenzenesulfonylamino)-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

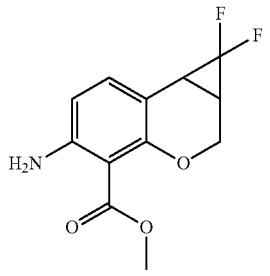


Prepared by proceeding in a similar manner to Intermediate 18, starting from methyl (1aRS,7bSR)-5-amino-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 61) and 2-bromo-4-fluorobenzene sulfonyl chloride, as a colourless foam.

^{1}H NMR ($CDCl_3$) δ: 9.58 (1H, s), 8.18 (1H, dd), 7.42 (1H, dd), 7.20 (1H, d), 7.13 (1H, d), 7.16-7.08 (1H, m), 4.38 (1H, d), 4.03 (1H, m), 3.91 (3H, s), 2.67 (1H, t), 2.32 (1H, m).

Intermediate 61

Methyl (1aRS,7bSR)-5-amino-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

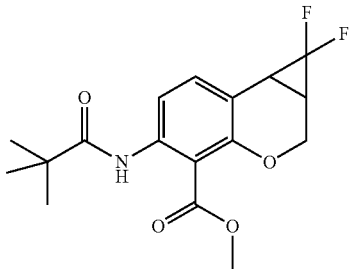


Prepared by proceeding in a similar manner to Intermediate 42, starting from methyl (1aRS,7bSR)-5-(2,2-dimethylpropionylamino)-1,1-difluoro-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (Intermediate 62) as an off white solid.

^{1}H NMR ($CDCl_3$) δ: 7.07 (1H, d), 6.30 (1H, d), 5.19-4.95 (2H, br s), 4.32 (1H, d), 4.11 (1H, m), 3.87 (3H, s), 2.60 (1H, t), 2.27 (1H, m).

Intermediate 62

Methyl (1aRS,7bSR)-5-(2,2-dimethylpropionylamino)-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

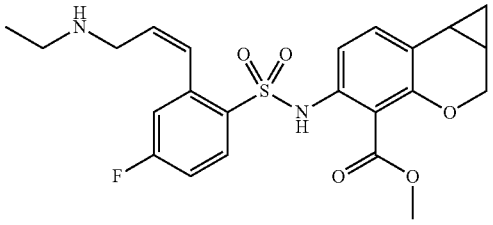


Methyl 7-(2,2-dimethylpropionylamino)-2H-chromene-8-carboxylate (Intermediate 45, 1.0 g) was dissolved in diglyme (30 mL) and the solution was heated to 160° C. Sodium chlorodifluoroacetate (4.27 g) was added in portions over 15 minutes with the final portion being washed in with diglyme (15 mL). On completion of the addition the mixture was heated at 180° C. for 15 minutes. After cooling, the mixture was poured into water and extracted with ethyl acetate, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and pentane with a gradient of 2.5-15% to give methyl (1aRS,7bSR)-5-(2,2-dimethylpropionylamino)-1,1-difluoro-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (0.66 g) as a colourless oil.

^{1}NMR ($CDCl_3$) δ: 9.86 (1H, br s), 8.12 (1H, d), 7.33 (1H, d), 4.41 (1H, d), 4.07 (1H, m), 3.92 (3H, s), 2.74 (1H, t), 2.34 (1H, m), 1.29 (9H, s).

Intermediate 63

Methyl (1aRS,7bSR)-5-[2-((Z)-3-ethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

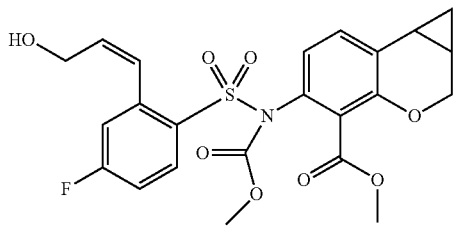


Methane sulfonic anhydride (0.09 g) was added to a stirred, cooled mixture of methyl (1aRS,7bSR)-5-{N-[methoxycarbonyl]-N-[2-((Z)-3-hydroxyprop-1-enyl)-4-fluorobenzenesulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 64, 0.17 g) and N,N-di-isopropyl-N-ethylamine (0.134 g) in DCM (10 mL) at 0° C. The temperature was allowed to rise to room temperature and the mixture was stirred for 2 hours. A solution of ethylamine (2M in toluene, 2 mL) was added and the resultant mixture was stirred at room temperature for 3 hours then diluted with water. The organic layer was separated, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give methyl (1aRS,7bSR)-5-[2((Z)-3-ethylaminoprop-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (0.09 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.89 (1H, dd), 7.35 (1H, d), 7.16 (1H, m), 7.08 (1H, d), 6.83 (1H, d), 6.58 (1H, d), 5.69 (1H, m), 4.17 (1H, d), 3.84-3.04 (2H, br s), 3.67 (3H, s), 3.58 (1H, d), 2.78 (2H, m), 1.83 (1H, m), 1.66 (1H, m), 1.04 (3H, t), 0.88 (1H, m), 0.64 (1H, m).

Intermediate 64

Methyl (1aRS,7bSR)-5-{N-[2-((Z)-3-hydroxyprop-1-enyl)-4-fluorobenzene-sulfonyl]-N-[methoxycarbonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

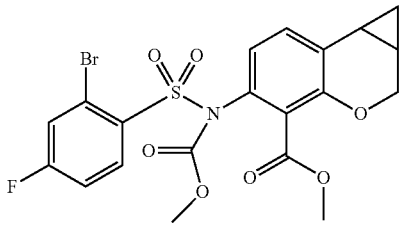


A mixture of methyl (1aRS,7bSR)-5-[N-(2-bromo-4-fluorobenzenesulfonyl)-N-(methoxycarbonyl)amino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 65, 0.6 g), (Z)-3-tributylstannanylprop-2-en-1-ol (Intermediate 12, 0.81 g), tris-(dibenzylideneacetone)dipalladium (0.1 g) and tri-tert-butylphosphonium tetrafluoroborate (0.07 g) in dioxane (18 mL) and DMSO (2 mL) was stirred at room temperature for 30 minutes. The resultant mixture was diluted with ethyl acetate and washed with water, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and petroleum ether with a gradient of 30-50% to give methyl (1aRS,7bSR)-5-{N-[2-((Z)-3-hydroxyprop-1-enyl)-4-fluorobenzenesulfonyl]-N-[methoxycarbonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (0.55 g) as an off-white solid.

^{1}H NMR ($CDCl_3$) δ: 8.19 (1H, m), 7.39 (1H, d), 7.16 (1H, m), 7.02 (1H, m), 6.96 (2H, m), 6.03 (1H, m), 4.41 (1H, m), 4.23 (2H, m), 3.88 (1H, dd), 3.71 (3H, 2s), 3.65 (3H, 2s), 2.06 (1H, m), 1.82 (1H, m), 1.25 (1H, m), 1.14 (1H, m).

Intermediate 65

Methyl (1aRS,7bSR)-5-[N-(2-bromo-4-fluorobenzenesulfonyl)-N-(methoxycarbonyl)amino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

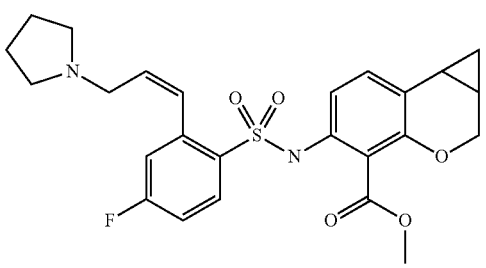


A solution of methyl (1aRS,7bSR)-5-(2-bromo-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 41, 1.7 g) in THF (20 mL) was added to a suspension of sodium hydride (70% oil dispersion, 0.2 g) in THF (10 mL). The resultant solution was stirred for 30 minutes then methyl chloroformate (0.53 g) was added. The resultant mixture was stirred at room temperature overnight. Saturated aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and petroleum ether (30%) to give methyl (1aRS,7bSR)-5-[N-(2-bromo-4-fluorobenzenesulfonyl)-N-(methoxycarbonyl)amino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (1.6 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 8.42 (1H, m), 7.48 (1H, dd), 7.37 (1H, d), 7.19 (2H, m), 4.42 (1H, m), 3.95 (1H, dd), 3.86 (3H, s,), 3.69 (3H, s), 2.06 (1H, m), 1.84 (1H, m), 1.16 (2H, m).

Intermediate 66

Methyl (1aRS,7bSR)-5-{2[(Z)-3-(pyrrolidin-1-yl) prop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

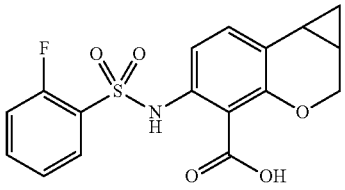


Prepared by proceeding in a similar manner to Intermediate 63, starting from methyl (1aRS,7bSR)-5-{N-[methoxycarbonyl]-N-[2-((Z)-3-hydroxyprop-1-enyl)-4-fluorobenzenesulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 64) and pyrrolidine as a brown oil.

LCMS (Method D) r/t 1.28 (M+H) 487

Intermediate 67

(1aRS,7bSR)-5-(2-Fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid

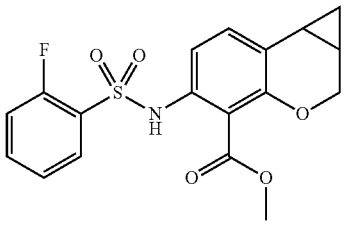


A mixture of methyl (1aRS,7bSR)-5-(2-Fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 68, 0.6 g) and lithium hydroxide monohydrate (1.5 g) in dioxane (45 mL) and water (13.8 mL) was stirred and heated at 100° C. overnight. After cooling, the mixture was concentrated under vacuum and the residue was diluted with water and acidified to pH3 with 1M hydrochloric acid. The precipitated solid was collected by filtration to give (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.58 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 13.05 (1H, br s), 9.96 (1H, s), 7.73 (2H, m), 7.45-7.31 (2H, m), 7.23 (1H, d), 6.64 (1H, d), 4.29 (1H, d), 3.74 (1H, d), 2.01 (1H, m), 1.80 (1H, m), 1.02 (1H, m), 0.81 (1H, m).

Intermediate 68

Methyl (1aRS,7bSR)-5-(2-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

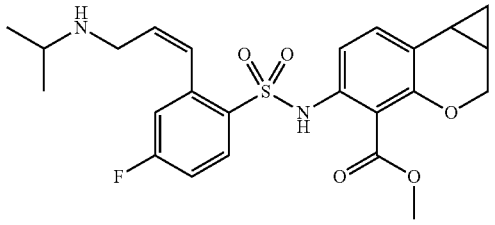


Prepared by proceeding in a similar manner to Intermediate 41, starting from methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 42) and 2-fluorobenzenesulfonyl chloride.

^{1}H NMR ($CDCl_3$) δ: 8.90 (1H, s), 7.84 (1H, dt), 7.53 (1H, m), 7.24-7.11 (4H, m), 4.34 (1H, d), 3.88 (3H, s), 3.80 (1H, dd), 1.91 (1H, m), 1.74 (1H, m), 1.02 (2H, m).

Intermediate 69

Methyl (1aRS,7bSR)-5-{2[(Z)-3-(propan-2-yl)aminoprop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

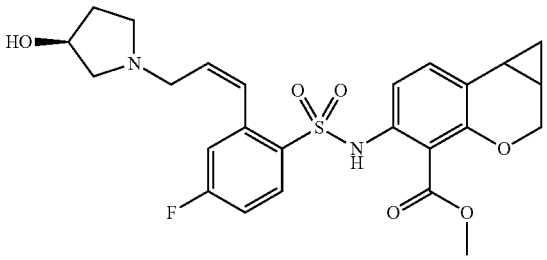


Prepared by proceeding in a similar manner to Intermediate 63, starting from methyl (1aRS,7bSR)-5-{N-[methoxycarbonyl]-N-[2-((Z)-3-hydroxyprop-1-enyl)-4-fluorobenzene-sulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 64) and 2-aminopropane.

LCMS (Method D) r/t 1.17 (M+H) 475.

Intermediate 70

Methyl (1aRS,7bSR)-5-{2[(Z)-3-((S)-3-hydroxypyrrolidin-1-yl)aminoprop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

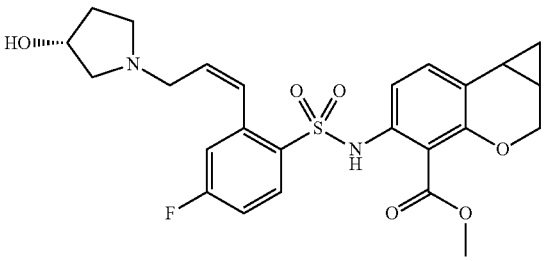


Prepared by proceeding in a similar manner to Intermediate 63, starting from methyl (1aRS,7bSR)-5-{N-[methoxycarbonyl]-N-[2-((Z)-3-hydroxyprop-1-enyl)-4-fluorobenzene-sulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 64) and (S)-3-hydroxypyrrolidine.

LCMS (Method D) r/t 1.14 (M+H) 503.

Intermediate 71

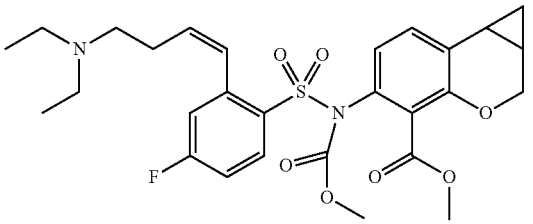
Methyl (1aRS,7bSR)-5-{2[(Z)-3-((R)-3-hydroxypyrrolidin-1-yl)aminoprop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrolcyclopropa[c]chromene-4-carboxylate



Prepared by proceeding in a similar manner to Intermediate 63, starting from methyl (1aRS,7bSR)-5-{N-[methoxycarbonyl]-N-[2-((Z)-3-hydroxyprop-1-enyl)-4-fluorobenzene-sulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 64) and (R)-3-hydroxypyrrolidine and used without further characterisation.

Intermediate 72

Methyl (1aRS,7bSR)-5-{N-(methoxycarbonly)-N-[2((Z)-4-diethylaminobut-1-enyl)-4-fluorobenzenesulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

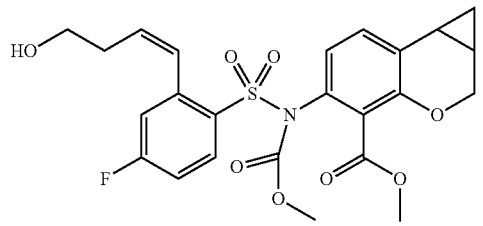


Methyl sulfonic anhydride (0.062 g) was added to a stirred, cooled mixture of methyl (1aRS,7bSR)-5-{N-[methoxycarbonyl]-N-[2-((Z)-4-hydroxybut-1-enyl)-4-fluorobenzenesulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 73, 0.12 g) and N,N-di-isopropyl-N-ethylamine (0.046 g) in DCM (15 mL) at 0° C. The resultant mixture was stirred at 0° C. for 20 minutes. Diethylamine (0.026 g) was added and the mixture was then stirred at room temperature for 24 hours. The mixture was diluted with water and extracted with DCM, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 2-10% to give methyl (1aRS,7bSR)-5-{N-(methoxycarbonyl)-N-[2((Z)-4-diethylaminobut-1-enyl)-4-fluorobenzenesulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (0.08 g) as alight yellow solid.

LCMS (Method D) r/t1.22 (M+H) 561.

Intermediate 73

Methyl (1aRS,7bSR)-5-{N-[methoxycarbonyl]-N-[2-((Z)-4-hydroxybut-1-enyl)-4-fluorobenzenesulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

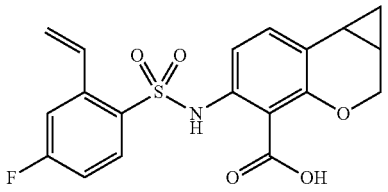


Prepared by proceeding in a similar manner to Intermediate 64, starting from methyl (1aRS,7bSR)-5-[N-(2-bromo-4-fluorobenzenesulfonyl)-N-(methoxycarbonyl)amino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 65) and (Z)-4-tributylstannanylprop-3-en-1-ol (prepared according to Miura et al, Organic Letters, 2005, 7(3) 503).

^{1}H NMR ($CDCl_3$) δ: 8.18 (1H, m), 7.38 (1H, d), 7.13 (3H, m), 6.96 (1H, d), 5.91 (1H, m), 4.44 (1H, m), 3.98 (1H, dd), 3.79 (3H, s), 3.75 (2H, m), 3.65 (3H, s), 2.49 (2H, m), 2.07 (1H, m), 1.81 (1H, m), 1.27 (1H, m), 1.15 (1H, m).

Intermediate 74

(1aRS,7bSR)-5-(4-Fluoro-2-vinylbenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid

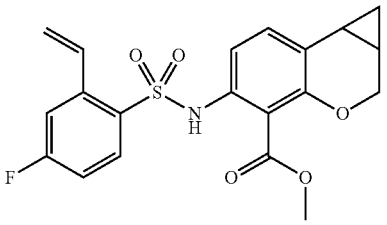


Lithium hydroxide (0.101 g) was added to a solution of methyl (1aRS,7bSR)-5-(4-fluoro-2-vinylbenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 75, 0.150 g) in a mixture of dioxane (3 mL) and water (0.6 mL) and the mixture was irradiated in the microwave at 130° C. for 30 minutes. After cooling, the mixture evaporated to dryness and the residue was acidified by addition of 10% aqueous citric acid (2 mL), extracted with DCM, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of methanol and DCM with a gradient of 0-10% to give (1aRS,7bSR)-5-(4-fluoro-2-vinylbenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid (0.0.35 g) as a glass.

^{1}H NMR ($CDCl_3$) δ: 11.69 (1H, br s), 8.10 (1H, dd), 7.50 (1H, dd), 7.31-7.17 (3H, m), 7.03 (1H, dt), 5.60 (1H, d), 5.50 (1H, d), 4.60 (1H, d), 4.04 (1H, d), 1.97 (1H, m), 1.81 (1H, m), 1.20 (1H, m), 0.99 (1H, m).

Intermediate 75

Methyl (1aRS,7bSR)-5-(4-fluoro-2-vinylbenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

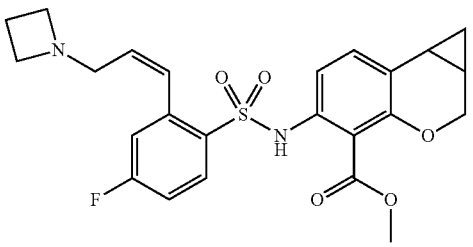


A mixture of methyl (1aRS,7bSR)-5-(2-bromo-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 41, 0.1 g), vinyl boronic acid pinacol ester (0.073 g), bis(triphenylphospine) palladium (II) chloride (0.034 g) and cesium carbonate (0.215 g) in dioxane (5 mL) and water (1 ml) was degassed and purged with argon then irradiated in a microwave at 130° C. for 20 minutes. After cooling, the mixture was partitioned between 1M hydrochloric acid and ethyl acetate. The organic layer was dried ($MgSO_4$) and filtered and the filtrate evaporated to dryness to give methyl (1aRS,7bSR)-5-(4-fluoro-2-vinylbenzenesulfonyl-amino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.15 g) as a yellow glass.

^{1}H NMR ($CDCl_3$) δ: 8.99 (1H, br s), 7.97 (1H, dd), 7.38 (1H, dd), 7.21 (1H, dd), 7.18 (1H, d), 7.05 (1H, d), 7.00 (1H, m), 5.59 (1H, d), 5.38 (1H, d), 4.32 (1H, d), 3.77 (4H, m), 1.90 (1H, dt), 1.71 (1H, m), 1.00 (2H, m).

Intermediate 76

Methyl (1aRS,7bSR)-5-{2[(Z)-3-(azetidin-1-yl)prop-1-enyl]-4-fluoro-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

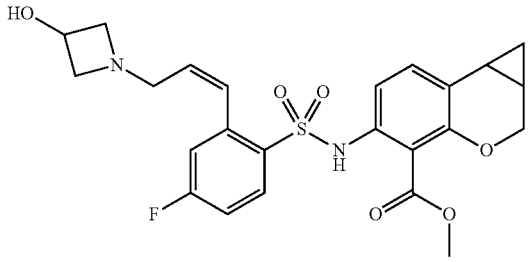


Prepared by proceeding in a similar manner to Intermediate 63, starting from methyl (1aRS,7bSR)-5-{N-[methoxycarbonyl]-N-[2-((Z)-3-hydroxyprop-1-enyl)-4-fluorobenzene-sulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 64) and azetidine as a yellow oil.

LCMS (Method D) r/t 1.17 (M+H) 473.

Intermediate 77

Methyl (1aRS,7bSR)-5-{2[(Z)-3-(3-hydroxyazetidin-1-yl)prop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

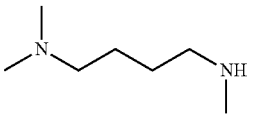


Prepared by proceeding in a similar manner to Intermediate 63, starting from methyl (1aRS,7bSR)-5-{N-[methoxycarbonyl]-N-[2-((Z)-3-hydroxyprop-1-enyl)-4-fluorobenzene-sulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 64) and 3-hydroxyazetidine as a yellow oil.

LCMS (Method D) r/t 1.15 (M+H) 489.

Intermediate 78

N-(4-Dimethylaminobutyl)-N-methylamine

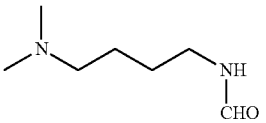


A solution of lithium aluminium hydride in THF (1M, 28 mL) was added dropwise to a stirred, cooled solution of N-(4-dimethylaminobutyl)formamide (Intermediate 79, 2.7 g) in THF (60 mL) while maintaining the temperature at 0° C. under an atmosphere of nitrogen. On completion of the addition, the mixture was stirred and heated at 75° C. for 2 hours. The reaction mixture was cooled to 0° C. and ethanol was added then the mixture was evaporated to dryness. The residue was diluted with a mixture of diethyl ether and DCM (30%) and the solid was filtered off. The filtrate was evaporated to dryness to give N-(4-dimethylaminobutyl)-N-methylamine (1.5 g) as a yellow oil.

^{1}H NMR ($CDCl_3$) δ: 2.56 (2H, m), 2.41 (3H, s), 2.25 (2H, m), 2.20 (6H, s), 1.47 (4H, m).

Intermediate 79

N-(4-Dimethylaminobutyl)formamide

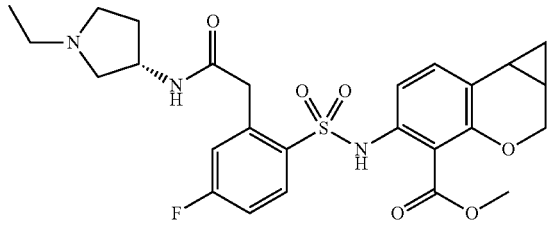


A solution of 4-dimethylaminobutylamine (3.0 g) in ethyl formate (30 mL) was stirred and heated at reflux under an atmosphere of nitrogen for 3 hours. After cooling, the mixture was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM (20%) to give N-(4-dimethylaminobutyl)formamide (2.7 g) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 8.14 (1H, s), 6.80 (1H, s), 3.50 (2H, m), 2.28 (2H, m), 2.20 (6H, s), 1.61 (4H, m).

Intermediate 80

Methyl (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-3-ylcarbamoyl)methyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

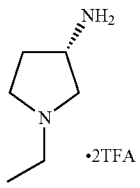


A solution of methyl (1aRS,7bSR)-5-(2-carboxymethyl-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 83, 0.180 g), (S)-1-ethylpyrrolidin-3-ylamine ditrifluoroacetic acid salt (Intermediate 81, 0.171 g), EDAC (0.144 g) and triethylamine (0.202 g) in DCM (5 mL) was allowed to stand at room temperature for 6 days then washed with water and filtered through a phase separator. The filtrate was directly purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-20% to give methyl (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-3-ylcarbamoyl)methyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.178 g) as an off-white foam.

LCMS (Method E) r/t 2.57 (M+H) 532

Intermediate 81

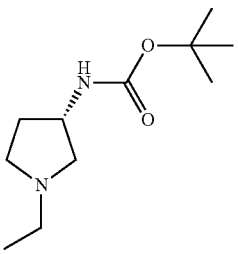
(S)-1-Ethylpyrrolidin-3-ylamine ditrifluoroacetic acid salt



A solution of tert-butyl ((S)-1-ethylpyrrolidin-3-yl)carbamate (Intermediate 82, 0.107 g) in a solution of trifluoroacetic acid (2 mL) and DCM (2 mL) was left to stand at room temperature for 30 minutes then concentrated in vacuo. The residue was azeotroped with toluene to give (S)-1-ethylpyrrolidin-3-ylamine ditrifluoroacetic acid salt (0.231 g) as a light brown gum which was used without further characterisation.

Intermediate 82

tert-Butyl ((S)-1-ethylpyrrolidin-3-yl)carbamate

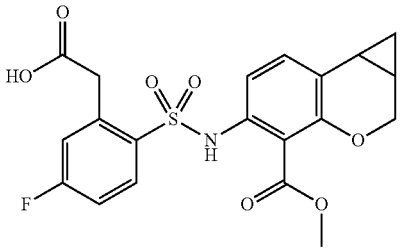


A mixture of tert butyl (S)-pyrrolidin-3-ylcarbamate (1.048 g), iodoethane (0.90 g) and potassium carbonate (1.55 g) in acetonitrile (15 mL) was stirred at room temperature for 17 hours then filtered. The filtrate was concentrated in vacuo and the residue was triturated with DCM and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-35% to give tert-butyl ((S)-1-ethylpyrrolidin-3-yl)carbamate (0.891 g) as a light coloured gum.

^{1}H NMR ($CDCl_3$) δ: 5.11 (1H, br, s), 4.29 (1H, br, s), 3.88 (1H, br, s), 3.18 (1H, br, s), 2.90 (2H, br, m), 2.76 (2H, br, m), 2.62 (1H, br, q), 2.38 (1H, m), 1.44 (9H, s), 1.28 (3H, t).

Intermediate 83

Methyl (1aRS,7bSR)-5-(2-carboxymethyl-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

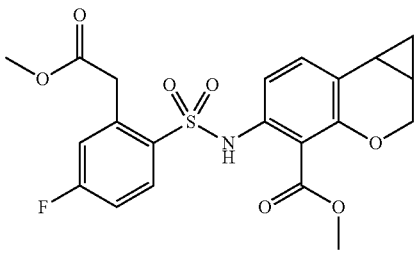


1M Sodium hydroxide solution (3 mL) was added to a solution of methyl (1aRS,7bSR)-5-(4-fluoro-2-methoxycarbonylmethylbenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 84, 0.438 g) in methanol (6 mL) and the mixture was heated at 50° C. for 2 hours. After cooling, the mixture was evaporated to dryness and the residue was dissolved in ethyl acetate and water and acidified with concentrated hydrochloric acid. The organic layer was dried (Na_2SO_4) and filtered and the filtrate was concentrated in vacuo, the residue was dissolved in toluene and re-evaporated to give methyl (1aRS,7bSR)-5-(2-carboxymethyl-4-fluorobenzene-sulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.422 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 8.83 (1H, br, s), 7.86 (1H, dd), 7.22 (1H, d), 7.01 (3H, m), 4.32 (1H, d), 4.00 (2H, m), 3.76 (1H, d), 3.73 (3H, s), 1.94 (1H, m), 1.73 (1H, m), 1.02 (2H, m).

Intermediate 84

Methyl (1aRS,7bSR)-5-[4-fluoro-2-(methoxycarbonylmethyl)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

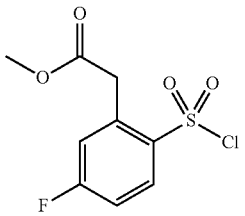


A solution of methyl (2-chlorosulfonyl-5-fluorophenyl)acetate (Intermediate 85, 0.293 g) and methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (Intermediate 42, 0.219 g) in pyridine (1 mL) and DCM (3 mL) was left to stand at room temperature for 4 days. The mixture was diluted with DCM, washed with 2M hydrochloric acid and filtered through a phase separator. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-40% to give methyl (1aRS,7bSR)-5-[4-fluoro-2-(methoxycarbonylmethyl)-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.438 g) as a colourless gum.

^{1}H NMR ($CDCl_3$) δ: 8.77 (1H, br, s), 7.84 (1H, dd), 7.22 (1H, d), 7.01 (3H, m), 4.33 (1H, d), 4.01 (2H, s), 3.79 (1H, d), 3.76 (3H, s), 3.69 (3H, s), 1.93 (1H, m), 1.73 (1H, m), 1.03 (2H, m).

Intermediate 85

Methyl (2-Chlorosulfonyl-5-fluorophenyl)acetate

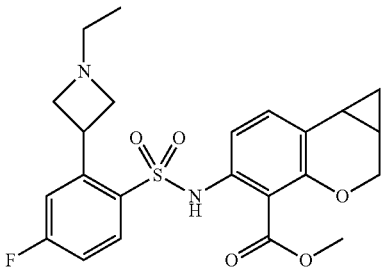


Methyl (3-fluorophenyl)acetate (1.51 g) was added dropwise to chlorosulphonic acid (7 mL) with stirring and ice cooling. The cooling bath was removed and the mixture was allowed to stand at room temperature for 16 hours before being carefully added to a mixture of ice and ethyl acetate. The organic layer was separated, washed with water, dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-20% to give methyl (2-chlorosulfonyl-5-fluorophenyl)acetate (1.42 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 8.16 (1H, dd), 7.21 (2H, m), 4.19 (2H, s), 3.76 (3H, s).

Intermediate 86

Methyl (1aRS,7bSR)-5-[2-(1-ethylazetidin-3-yl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

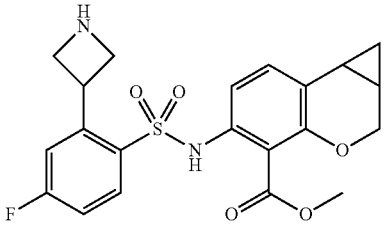


A mixture of methyl (1aRS,7bSR)-5-[2-(azetidin-3-yl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 87, 0.216 g), iodoethane (0.078 g) and potassium carbonate (0.138 g) in acetonitrile (5 mL) was stirred at room temperature for 18 hours. The mixture was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-15% to give methyl (1aRS,7bSR)-5-[2-(1-ethylazetidin-3-yl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (0.051 g).

^{1}H NMR ($CDCl_3$) δ: 7.97 (1H, dd), 7.62 (1H, dd), 7.24 (1H, d), 6.99 (1H, dt), 6.96 (1H, d), 4.35 (1H, d), 4.31 (1H, m), 3.79 (3H, s), 3.77 (1H, d), 3.58 (2H, m), 3.22 (2H, br, m), 2.53 (2H, q), 1.93 (1H, m), 1.74 (1H, q), 0.99 (5H, m).

Intermediate 87

Methyl (1aRS,7bSR)-5-[2-(azetidin-3-yl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

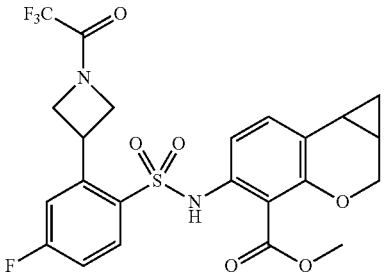


A mixture of methyl (1aRS,7bSR)-5-{4-fluoro-2-[1-(2,2,2-trifluoroacetyl)azetidin-3-yl]benzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 88, 0.294 g) and potassium carbonate (0.155 g) in methanol (5 mL) and water (0.5 mL) was stirred at room temperature for 45 minutes. The mixture was concentrated in vacuo and the residue was triturated with 10% methanol in DCM and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-40% to give methyl (1aRS,7bSR)-5-[2-(azetidin-3-yl)-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.216 g) as a pale yellow foam.

^{1}H NMR ($CDCl_3$) δ: δ: 7.94 (1H, dd), 7.54 (1H, dd), 7.27 (1H, d), 7.09 (1H, dt), 6.99 (1H, d), 4.87 (1H, m), 4.32 (3H, m), 4.12 (2H, t), 3.78 (1H, m), 3.73 (3H, s), 1.94 (1H, m), 1.73 (1H, m), 0.99 (2H, m).

Intermediate 88

Methyl (1aRS,7bSR)-5-{4-fluoro-2-[1-(2,2,2-trifluoroacetyl)azetidin-3-yl]benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

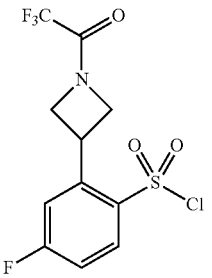


A solution of methyl 4-fluoro-2-[1-(2,2,2-trifluoroacetyl) azetidin-3-yl]benzenesulfonyl chloride (Intermediate 89, 0.192 g) and methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 42, 0.122 g) in pyridine (1 mL) and DCM (3 mL) was left to stand at room temperature for 18 hours. The mixture was diluted with DCM, washed with 1M hydrochloric acid and filtered through a phase separator. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-30% to give methyl (1aRS, 7bSR)-5-{4-fluoro-2-[1-(2,2,2-trifluoro-acetyl)azetidin-3-yl]benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (0.294 g) as a colourless gum.

^{1}H NMR ($CDCl_3$) δ: 8.99 (1H, br, s), 7.99 (1H, m), 7.81 (2H, m), 7.06 (2H, m), 4.68 (2H, m), 4.41 (1H, m), 4.34 (1H, d), 4.19 (1H, m), 4.08 (1H, m), 3.79 (1H, m), 3.72 (3H, s), 1.94 (1H, m), 1.75 (1H, m), 1.02 (2H, m).

Intermediate 89

4-Fluoro-2-[1-(2,2,2-trifluoroacetyl)-azetidin-3-yl] benzenesulfonyl chloride

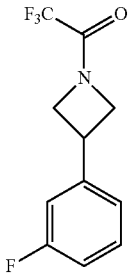


Chlorosulphonic acid (5 mL) was added to 2,2,2-trifluoro-1-[3-(3-fluorophenyl)azetidin-1-yl]ethanone (Intermediate 90, 1.15 g) with stirring and ice cooling. The mixture was stirred for 1 hour then poured carefully onto a mixture of ice and ethyl acetate. The organic layer was washed with water and concentrated in vacuo. The residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-20% to give 4-fluoro-2-[1-(2,2,2-trifluoroacetyl)azetidin-3-yl]benzenesulfonyl chloride (0.910 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 8.22 (1H, m), 7.51 (1H, dd), 7.26 (1H, m), 4.95 (2H, m), 4.70 (1H, t), 4.42 (1H, m), 4.31 (1H, m).

Intermediate 90

2,2,2-Trifluoro-1-[3-(3-fluorophenyl)azetidin-1-yl] ethanone

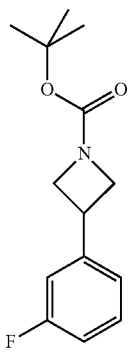


A solution of tert-butyl 3-(3-fluorophenyl)azetidine-1-carboxylate (Intermediate 92, 2.51 g) in trifluoroacetic acid (15 mL) and DCM (15 mL) was left to stand at room temperature for 30 minutes. The mixture was concentrated in vacuo and the residue was azeotroped with toluene. The residue was dissolved in DCM (15 mL) and pyridine (5 mL) and trifluoroacetic anhydride (3.15 g) was added. The mixture was left to stand at room temperature for 30 minutes, then washed with 1M hydrochloric acid and filtered through a phase separator. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-20% to give 2,2,2-trifluoro-1-[3-(3-fluorophenyl)azetidin-1-yl]ethanone (2.31 g) as a light brown oil.

^{1}H NMR ($CDCl_3$) δ: 7.36 (1H, m), 7.10 (1H, d), 7.02 (2H, m), 4.81 (1H, t), 4.57 (1H, t), 4.44 (1H, dd), 4.20 (1H, dd), 3.96 (1H, m).

Intermediate 91

tert-Butyl 3-(3-fluorophenyl)azetidine-1-carboxylate

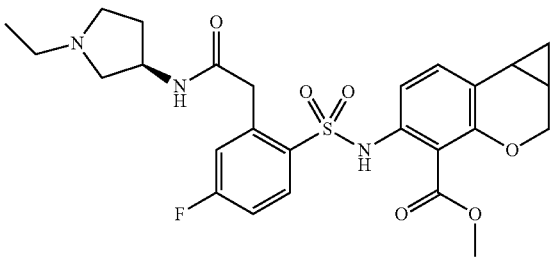


A solution of 1,2-dibromoethane (0.30 g) in anhydrous DMF (25 ml) was stirred with zinc dust (1.39 g) at 70° C. for 10 minutes then cooled to room temperature and chlorotrimethylsilane was (0.155 g) added. The resultant mixture was stirred at room temperature for 45 minutes. tert-Butyl 3-iodoazetidine-1-carboxylate (5 g) added and stirring was continued at 40° C. for 45 minutes then a solution of 3-fluoroiodobenzene (4.08 g), tris(dibenzylideneacetone) dipalladium(0) (0.325 g) and tris(2-furyl)phosphine (0.165 g) in DMF (15 mL) was added and the mixture was stirred at 70° C. for 3 hours. After cooling, the mixture was diluted with water and ethyl acetate and filtered through celite. The organic layer was washed twice with water, dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-10%. The crude product was further purified by chromatography on silica, eluting with a mixture of DCM and cyclohexane with a gradient of 0-100% to give tert-butyl 3-(3-fluorophenyl)azetidine-1-carboxylate (2.52 g) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ: 7.32 (1H, m), 6.90-7.11 (3H, m), 4.34 (2H, t), 3.95 (2H, dd), 3.72 (1H, m), 1.48 (9H, s).

Intermediate 92

Methyl (1aRS,7bSR)-5-{2-[((R)-1-ethylpyrrolidin-3-ylcarbamoyl)methyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

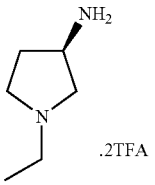


Prepared by proceeding in a similar manner to Intermediate 80, starting from methyl (1aRS,7bSR)-5-(2-carboxymethyl-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 83) and (R)-1-ethylpyrrolidin-3-ylamine ditrifluoroacetic acid salt (Intermediate 93) as a light brown foam.

LCMS (Method E) r/t 2.57 (M+H) 532.

Intermediate 93

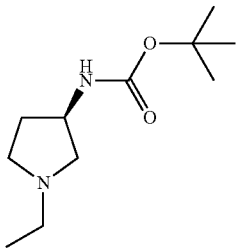
(R)-1-Ethylpyrrolidin-3-ylamine ditrifluoroacetic acid salt



Prepared by proceeding in a similar manner to Intermediate 81, starting from tert-butyl ((R)-1-ethylpyrrolidin-3-yl) carbamate as a light brown gum which was used without further characterisation.

Intermediate 94

tert-Butyl ((R)-1-ethylpyrrolidin-3-yl)carbamate

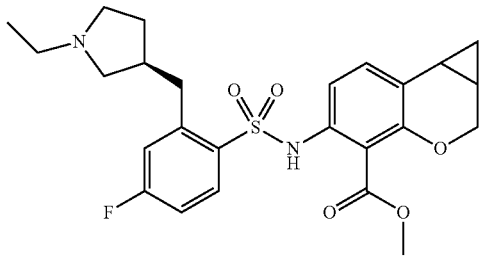


Prepared by proceeding in a similar manner to intermediate 82, starting from tert butyl (R)-pyrrolidin-3-yl-carbamate and iodoethane as a light coloured gum.

^{1}H NMR ($CDCl_3$) δ: 5.09 (2H, br, s), 4.25 (1H, br, s), 3.08 (1H, br, s), 2.82 (2H, br, m), 2.69 (2H, br, q), 2.52 (1H, br, q), 2.35 (1H, m), 1.44 (9H, s), 1.21 (3H, t).

Intermediate 95

Methyl (1aS,7bR)-5-[2-((R)-1-ethylpyrrolidin-3-ylmethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

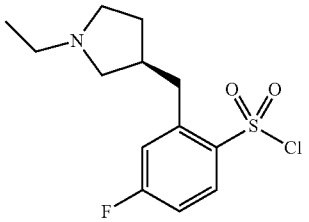


A solution of methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 42, 0.257 g) in DCM (10 mL) and pyridine (5 mL) was treated with a solution of 2-((R)-1-ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl chloride (Intermediate 96, 0.36 g) in DCM (10 mL) and the mixture was stirred at room temperature overnight. The resultant mixture was evaporated to dryness and the residue was re-dissolved in DCM, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-10%, then flushed with 100% methanol to give methyl (1aS,7bR)-5-[2-((R)-1-ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.13 g) as a gum.

^{1}H NMR ($CDCl_3$) δ: 7.88 (1H, br t), 7.23 (1H, d), 7.13 (1H, br d), 6.98 (2H, m), 4.33 (1H, d), 3.79 (1H, d), 3.77 (3H, s), 3.20-2.90 (6H, m) 2.24 (1H, br s), 2.04-1.18 (3H, br s), 1.93 (2H, dt), 1.74 (1H, q), 1.45 (3H, t), 1.02 (2H, m).

Intermediate 96

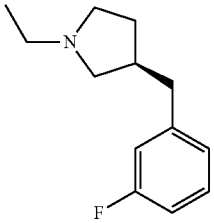
2-((R)-1-Ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl chloride



A solution of (R)-1-ethyl-3-(3-fluorobenzyl)pyrrolidine (Intermediate 97, 0.24 g) in DCE (1.2 mL) was added carefully to chlorosulfonic acid and the mixture was stirred at room temperature for 2 hours. The mixture was carefully poured into iced water and extracted with DCM, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give 2-((R)-1-ethyl-pyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl chloride (0.36 g) as an oil which was used without further charactersiation.

Intermediate 97

(R)-1-Ethyl-3-(3-fluorobenzyl)-pyrrolidine

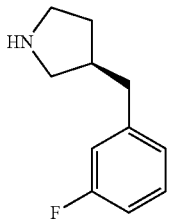


Ethyl bromide (0.22 g) was added to a suspension of 3-(R)-(3-fluorobenzyl)pyrrolidine (Intermediate 98, 0.36 g) and potassium carbonate (0.55 g) in acetonitrile and the mixture was stirred at room temperature for 2.5 hours. The mixture was diluted with ethyl acetate, filtered and the filtrate was evaporated to dryness. The residue was triturated with DCM, the solvent was decanted off and evaporated to dryness to give (R)-1-ethyl-3-(3-fluorobenzyl)pyrrolidine (0.24 g) as an oil.

^{1}H NMR ($CDCl_3$) δ: 7.22 (1H, m), 6.95 (1H, d), 6.88 (2H, m), 2.73-2.60 (4H, m), 2.52-2.38 (4H, m), 2.17 (1H, dd), 1.97 (1H, m), 1.49 (1H, m), 1.09 (3H, t).

Intermediate 98

3-(R)-(3-Fluorobenzyl)pyrrolidine

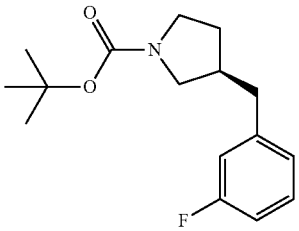


Trifluoroacetic acid (10 mL) was added to a solution of tert butyl (R)-3-(3-fluorobenzyl)-pyrrolidine-1-carboxylate (Intermediate 99, 0.515 g) in DCM (10 mL) and the mixture was stirred for 1 hour at room temperature. The mixture was evaporated to dryness and the residue was partitioned between DCM and saturated aqueous $NaHCO_3$. The organic extract was separated, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give 3-(R)-(3-fluoro-benzyl) pyrrolidine (0.402 g) as an oil.

^{1}H NMR ($CDCl_3$) δ: 7.30-7.23 (2H, m), 6.94 (1H, d), 6.88 (1H, dt), 3.45-3.16 (3H, br m), 2.90 (1H, m), 2.76 (2H, d), 2.63 (1H, m), 2.12 (1H, m), 1.74 (1H, m).

Intermediate 99

tert-Butyl (R)-3-(3-fluorobenzyl)pyrrolidine-1-carboxylate

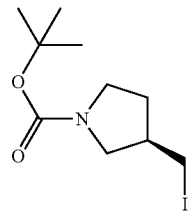


Nickel Iodide (0.147 g), trans-2-aminocyclohexanol HCl salt (0.74 g), 3-fluorobenzene boronic acid (0.78 g) and sodium hexamethyldisilazide (0.208 g) were placed in a sealed tube and degassed and purged with argon. Isopropanol (8 mL) was added and the mixture was stirred at 40° C. for 5 minutes. A solution of tert-butyl (R)-3-iodomethylpyrrolidine-1-carboxylate (Intermediate 100, 1.44 g) in isopropanol (8 mL) was added and the mixture was stirred and heated at 70° C. overnight. After cooling, the mixture was diluted with ethyl acetate, filtered through Celite and the filtrate was evaporated to dryness. The residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-60% to give tert-butyl (R)-3-(3-fluorobenzyl)pyrrolidine-1-carboxylate (0.515 g) as an oil.

^{1}H NMR ($CDCl_3$) δ: 7.27-7.21 (2H, m), 6.95-6.84 (2H, m), 3.46 (2H, m), 3.26 (1H, m), 2.98 (1H, dd), 2.67 (2H, m), 2.40 (1H, m), 1.92 (1H, m), 1.58 (1H, m), 1.46 (9H, s).

Intermediate 100

tert-Butyl (R)-3-iodomethylpyrrolidine-1-carboxylate



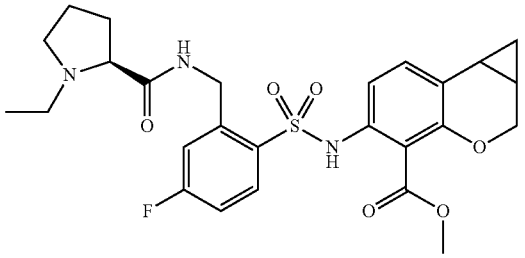
Iodine (1.91 g) was added in portions to a vigorously stirred, ice cooled suspension of imidazole (0.681 g) and triphenylphosphine (1.97 g) in diethyl ether (12 mL). The mixture was then stirred for 10 minutes before a solution of tert butyl (R)-3-hydroxymethylpyrrolidine-1-carboxylate (1 g) in dioxane (6 mL) was added dropwise. The resulting mixture was stirred at room temperature overnight, then diluted with diethyl ether and filtered. The solid was washed with diethyl ether and the combined filtrate was evaporated to dryness. The residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and pentane with

a gradient of 0-20% to give tert-butyl (R)-3-iodomethylpyrrolidine-1-carboxylate (1.44 g) as an oil.

^{1}H NMR ($CDCl_3$) δ: 3.64-3.46 (2H, m), 3.33 (1H, m), 3.19 (2H, d), 3.02 (1H, dd), 2.49 (1H, m), 2.07 (1H, m), 1.65 (1H, m), 1.46 (9H, s).

Intermediate 101

Methyl (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-2-yl)cabonyl-aminomethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

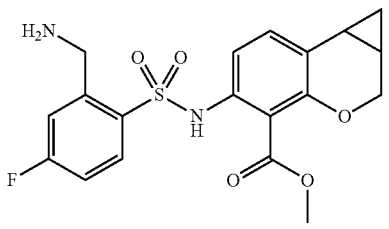


A mixture of methyl (1aRS,7bSR)-5-(2-aminomethyl-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 102, 0.515 g), HATU (0.483 g), (S)—N-ethylpyrrolidine-2-carboxylic acid (Intermediate 106, 0.182 g) and N,N-di-isopropyl-N-ethylamine (0.328 g) in dry DMF (25 mL) was stirred at room temperature for 2 hours. The mixture was concentrated under vacuum and the residue was diluted with water and extracted with ethyl acetate, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM, with a gradient of 1-2% to give methyl (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-2-yl) cabonyl-aminomethyl]-4-fluorobenzenesulfonylamino}-1, 1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (0.505 g) as a glassy solid.

^{1}H NMR ($CDCl_3$) δ: 9.2-8.9 (1H, br s), 7.82 (2H, m), 7.24 (2H, m), 7.00 (1H, dt), 6.95 (1H, dd), 4.75 (2H, m), 4.33 (1H, d), 3.99 (1H, br s), 3.79 (1H, m), 3.77 (3H, s), 3.67 (1H, m), 3.15-2.87 (3H, m), 2.48 (1H, m), 2.02 (2H, m), 1.93 (2H, m), 1.74 (1H, m), 1.20 (3H, m), 1.02 (2H, m).

Intermediate 102

Methyl (1aRS,7bSR)-5-(2-aminomethyl)-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

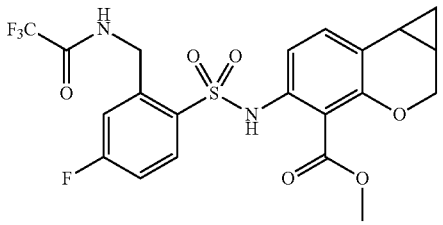


A solution of potassium carbonate (2.1 g) in water was added to a solution of methyl (1aRS,7bSR)-5-(4-fluoro-2-trifluoroacetylaminomethyl)benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 103, 1.53 g) in methanol (50 mL) and the resultant mixture was stirred and heated at 45° C. for 4 hours. After cooling, the mixture was concentrated under vacuum and the residue was diluted with water and saturated with salt. The resultant solid was collected by filtration, washed with water and ethyl acetate then dried under vacuum at 50° C. to give methyl (1aRS,7bSR)-5-(2-aminomethyl)-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylate (1.06 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 8.52 (1H, br s), 7.99 (1H, dd), 7.32 (2H, m), 6.89 (1H, d), 6.74 (1H, d), 4.32 (2H, s), 4.17 (1H, d), 3.70 (3H, s), 3.64 (1H, d), 1.82 (1H, m), 1.65 (1H, m), 0.89 (1H, m), 0.61 (1H, m).

Intermediate 103

Methyl (1aRS,7bSR)-5-(4-fluoro-2-trifluoroacetylaminomethyl)benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

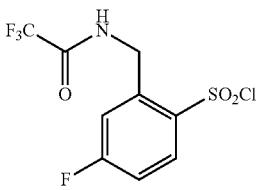


Methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 42, 0.972 g) was added to a solution of 4-fluoro-2-(trifluoroacetylaminomethyl)-benzenesulfonyl chloride (Intermediate 104, 1.53 g) in DCM (25 mL) and pyridine (6 mL). The resultant mixture was stirred at room temperature for 2 hours. The mixture was diluted with DCM, washed with water, HCl (1M), water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and pentane with a gradient of 5-30% to give methyl (1aRS,7bSR)-5-(2-trifluoroacetylaminomethyl)-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (1.76 g) as a glassy foam.

^{1}H NMR ($CDCl_3$) δ: 9.04 (1H, br s), 7.83 (1H, dd), 7.49 (1H, br t), 7.30 (1H, dd), 7.29 (1H, d), 7.09 (1H, d), 7.06 (1H, dt), 4.61 (2H, d), 4.34 (1H, d), 3.78 (1H, dd), 3.73 (3H, s), 1.95 (1H, m), 1.75 (1H, m), 1.04 (2H, m).

Intermediate 104

4-Fluoro-2-(trifluoroacetylaminomethyl)benzenesulfonyl chloride

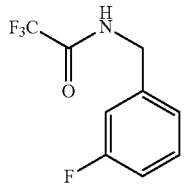


3-Fluoro-N-trifluoroacetylbenzylamine (Intermediate 105, 1.11 g) was added portionwise to chlorosulfonic acid (5 mL), while stirring and cooling in an ice bath. On completion of the addition, the ice bath was removed and the mixture was allowed to come to room temperature then heated to 70° C. for 3 hours. After cooling, the mixture was slowly added to ice and the resultant suspension was extracted with ethyl acetate, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give 4-fluoro-2-(trifluoroacetylaminomethyl)benzenesulfonyl chloride (1.53 g) as a brown solid.

^{1}H NMR ($CDCl_3$) δ: 8.18 (1H, dd), 7.47 (1H, m), 7.29 (1H, m), 7.18 (1H, br s), 4.92 (2H, d).

Intermediate 105

3-Fluoro-N-trifluoroacetylbenzylamine

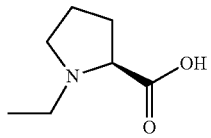


Trifluoroacetic anhydride (5.05 g) was added dropwise to an ice-cooled solution of 3-fluorobenzylamine (2.5 g) and triethylamine (2.22 g) in ethyl acetate (75 mL) while maintaining the temperature below 10° C. The mixture was stirred at 0-5° C. for 1 hour then allowed to warm to room temperature and stirred for 2 hours. Water was added and the layers were separated. The organic layer was washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give 3-fluoro-N-trifluoroacetylbenzylamine (4.58 g) as an oil which crystallised on standing to a white solid.

^{1}H NMR ($CDCl_3$) δ: 7.34 (1H, m), 7.03 (3H, m), 6.72 (1H, br s), 4.53 (2H, d).

Intermediate 106

(S)—N-Ethylpyrrolidine-2-carboxylic acid

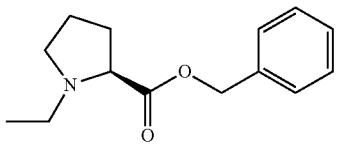


Palladium on carbon (10%, 0.2 g) was added to a solution of benzyl (S)—N-ethylpyrrolidine-2-carboxylate (Intermediate 107, 0.603 g) under an atmosphere of nitrogen. The mixture was then hydrogenated at 4 Bar for 3 hours. The mixture was filtered through Celite and the filtrate was evaporated to dryness to give (S)—N-ethylpyrrolidine-2-carboxylic acid (0.378 g) as a straw coloured gummy solid.

^{1}H NMR ($CDCl_3$) δ: 4.01 (1H, m), 3.78 (1H, m), 3.31 (1H, m), 3.18 (1H, m), 2.87 (1H, m), 2.38 (1H, m), 2.27 (1H, m), 2.02 (2H m), 1.39 (3H, t).

Intermediate 107

Benzyl (S)—N-ethylpyrrolidine-2-carboxylate hydrochloride

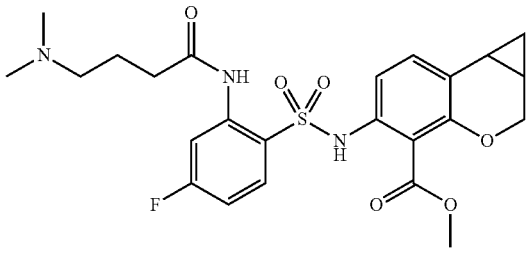


Iodoethane (1.34 g) was added to a mixture of benzyl (S)-pyrrolidine-2-carboxylate (1.0 g) and potassium carbonate (1.77 g) in dry DMF (7 mL) and the resultant mixture was stirred at room temperature for 3 days. The mixture was diluted with water, extracted with ethyl acetate, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and pentane with a gradient of 10-20% to give benzyl (S)—N-ethylpyrrolidine-2-carboxylate (0.643 g) as a pale straw coloured oil.

^{1}H NMR ($CDCl_3$) δ: 7.35 (5H, m), 5.17 (2H, s), 3.19 (2H, m), 2.74 (1H, m), 2.45 (1H, m), 2.34 (1H, m), 2.12 (1H, m) 1.93 (2H, m), 1.81 (1H, m), 1.10 (3H, t).

Intermediate 108

Methyl (1aRS,7bSR)-5-[2-(4-dimethylaminobutyrylamino)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

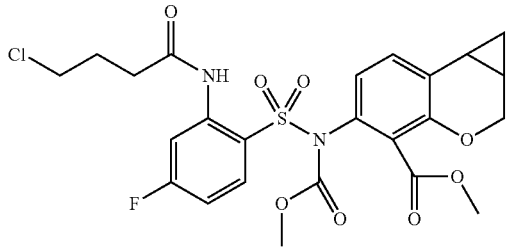


A mixture of methyl (1aRS,7bSR)-5-{N-[methoxycarbonyl]-N-[2-(4-chlorobutyryl-amino)-4-fluorobenzenesulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 109, 0.15 g) and dimethylamine (30% aqueous solution, 5 mL) in acetonitrile (10 mL) was stirred and heated at 40° C. for 10 hours. After cooling, the mixture was concentrated under vacuum and the residue was extracted with a mixture of ethyl acetate and THF (50%), dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by thick layer chromatography on silica, eluting with a mixture of methanol and DCM (10%) to give methyl (1aRS,7bSR)-5-[2-(4-dimethylaminobutyrylamino)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (0.14 g) as a yellow oil.

LCMS (Method D) r/t 1.24 (M+H) 506.

Intermediate 109

Methyl (1aRS,7bSR)-5-{N-[methoxycarbonyl]-N-[2-(4-chlorobutyryl-amino)-4-fluorobenzenesulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

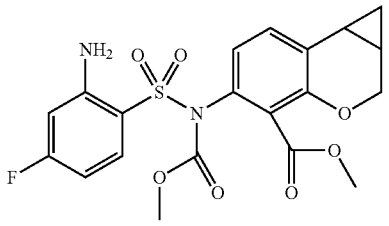


4-Chlorobutyryl chloride (3.0 g) was added to a stirred, cooled solution of methyl (1aRS,7bSR)-5-[N-(methoxycarbonyl)-N-(2-amino-4-fluorobenzenesulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 110, 0.135 g) and triethylamine (1.0 g) in THF (10 mL) at 0° C. On completion of the addition, the mixture was stirred at room temperature for 4 hours. Saturated aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and petroleum ether, with a gradient of 20-25% to give methyl (1aRS,7bSR)-5-{N-[methoxycarbonyl]-N-[2-(4-chlorobutyrylamino)-4-fluoro-benzenesulfonyl]amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (0.15 g) as a yellow oil.

LCMS (Method D) r/t 1.72 (M+H) 555.

Intermediate 110

Methyl (1aRS,7bSR)-5-[N-(methoxycarbonyl)-N-(2-amino-4-fluorobenzene-sulfonyl)amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

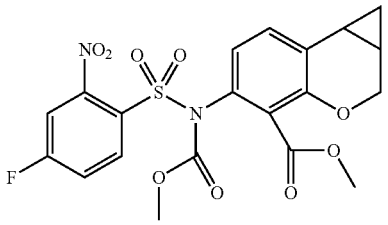


A mixture of methyl (1aRS,7bSR)-5-[N-(methoxycarbonyl)-N-(4-fluoro-2-nitrobenzene-sulfonyl)amino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (Intermediate 111, 0.2 g), zinc (0.54 g) and acetic acid (0.5 g) in ethanol (20 mL) was stirred and heated at reflux for 1 hour. After cooling, the solid was filtered off and the filtrate was evaporated to dryness. The residue was treated with saturated aqueous sodium bicarbonate and extracted with ethyl acetate, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and petroleum ether with a gradient of 30-50% to give methyl (1aRS,7bSR)-5-[N-(methoxycarbonyl)-N-(2-amino-4-fluorobenzene-sulfonyl)amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.15 g) as a white solid.

^1H NMR ($CDCl_3$) δ: 7.74 (1H, m), 7.36 (1H, d), 6.95 (1H, d), 6.47 (1H, m), 6.39 (1H, d), 5.37 (2H, m), 4.42 (1H, m), 3.91 (1H, d), 3.74 (3H, 2s), 3.70 (3H, 2s), 2.06 (1H, m), 1.84 (1H, m), 1.28 (1H, m), 1.15 (1H, m).

Intermediate 111

Methyl (1aRS,7bSR)-5-[N-(methoxycarbonyl)-N-(4-fluoro-2-nitrobenzene-sulfonyl)amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

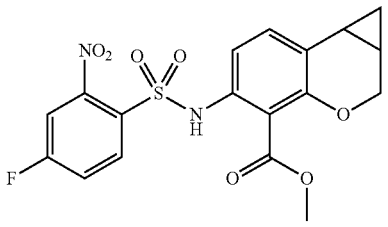


A solution of methyl (1aRS,7bSR)-5-(4-fluoro-2-nitrobenzenesulfonylamino)-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (Intermediate 112, 0.25 g) in THF (10 mL) was added dropwise with stirring to a cooled suspension of sodium hydride (0.1 g) in THF (5 mL) at 0° C. On completion of the addition, the mixture was stirred at room temperature for 30 minutes. Methyl chloroformate (0.3 g) was added dropwise and the mixture was stirred at room temperature for 1.5 hours. Saturated aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and petroleum ether to give methyl (1aRS,7bSR)-5-[N-(methoxycarbonyl)-N-(4-fluoro-2-nitrobenzenesulfonyl)amino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (0.2 g) as a white solid.

LCMS (Method D) r/t 1.58 (M+H) 481.

Intermediate 112

Methyl (1aRS,7bSR)-5-(4-fluoro-2-nitrobenzene-sulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

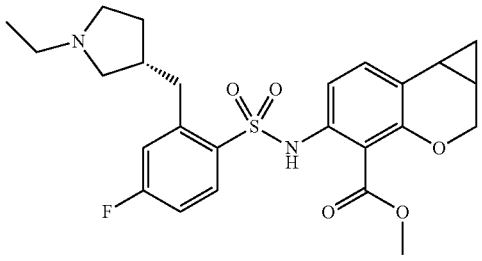


A mixture of methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 42, 0.1 g), 4-fluoro-2-nitrobenzenesulfonyl chloride (0.115 g) and pyridine (2 mL) in DCM (5 mL) was stirred at room temperature overnight. The mixture was concentrated under vacuum and the residue was partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4) and filtered and the filtrate was evaporated to dryness. The residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and petroleum ether (20%) to give methyl (1aRS,7bSR)-5-(4-fluoro-2-nitrobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.11 g) as a yellow oil.

^{1}H NMR ($CDCl_3$) δ: 8.56 (1H, br s), 7.92 (1H, m), 7.55 (1H, dd), 7.31 (2H, m), 7.24 (1H, m), 4.34 (1H, d), 3.85 (3H, s), 3.82 (1H, d), 1.98 (1H, m), 1.74 (1H, m), 1.08 (2H, m).

Intermediate 113

Methyl (1aS,7bR)-5-[2-((S)-1-ethyl-pyrrolidin-3-ylmethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

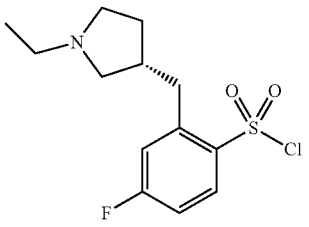


A solution of methyl 5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 42, 0.19 g) in DCM (10 mL) and pyridine (3.5 mL) was treated with a solution of 2-((S)-1-ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl chloride (Intermediate 114, 0.26 g) in DCM (5 mL) and the mixture was stirred and heated at 40° C. for 1 hour. The resultant mixture was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of DCM and methanol with a gradient of 0-25%, then flushed with 100% methanol to give methyl (1aS,7bR)-5-[2-((S)-1-ethylpyrrolidin-3-ylmethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.107 g) as a gum.

LCMS (Method A) r/t 2.29 (M+H) 489.

Intermediate 114

2-((S)-1-Ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl chloride

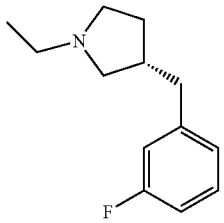


Prepared by proceeding in a similar manner to Intermediate 96, starting from (S)-1-ethyl-3-(3-fluorobenzyl)pyrrolidine (Intermediate 115).

LCMS (Method A) r/t 1.95 (M+H) 308.

Intermediate 115

(S)-1-Ethyl-3-(3-fluorobenzyl)pyrrolidine

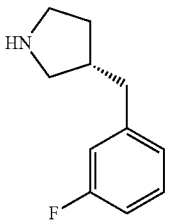


Prepared by proceeding in a similar manner to Intermediate 97 starting with 3-(S)-(3-fluoro-benzyl)pyrrolidine (Intermediate 116).

^{1}H NMR ($CDCl_3$) δ: 7.22 (1H, m), 6.95 (1H, d), 6.88 (2H, m), 2.81-2.62 (4H, br m), 2.61-2.39 (4H, br m), 2.21 (1H, br s), 1.99 (1H, m), 1.52 (1H, m), 1.11 (3H, t).

Intermediate 116

3-(S)-(3-Fluorobenzyl)-pyrrolidine

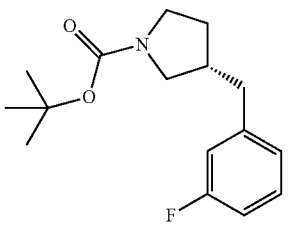


Prepared by proceeding in a similar manner to Intermediate 98 starting with tert-butyl (S)-3-(3-fluorobenzyl)-pyrrolidine-1-carboxylate (intermediate 117).

^{1}H NMR ($CDCl_3$) δ: 7.27 (1H, m), 6.96-6.84 (3H, m), 3.32 (1H, m), 3.25 (1H, dd), 3.16 (1H, m), 2.83 (1H, m), 2.73 (2H, d), 2.58 (1H, m), 2.08 (1H, m), 1.68 (1H, m).

Intermediate 117

tert-Butyl (S)-3-(3-fluorobenzyl)-pyrrolidine-1-carboxylate

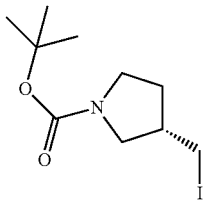


Prepared by proceeding in a similar manner to Intermediate 99 starting with tert-butyl (S)-3-iodomethylpyrrolidine-1-carboxylate (Intermediate 118).

^{1}H NMR ($CDCl_3$) δ: 7.27 (1H, m), 6.97-6.83 (3H, m), 3.46 (2H, m), 3.25 (1H, m), 2.98 (1H, m), 2.67 (2H, m), 2.40 (1H, m), 1.91 (1H, m), 1.58 (1H, m), 1.45 (9H, s).

Intermediate 118

tert-Butyl (S)-3-iodomethylpyrrolidine-1-carboxylate

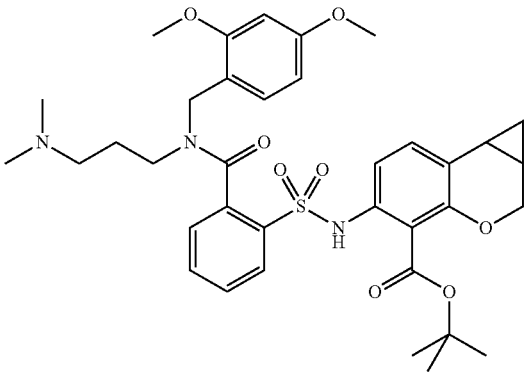


Prepared by proceeding in a similar manner to Intermediate 100 starting with tert-butyl (S)-3-hydroxymethylpyrrolidine-1-carboxylate.

^{1}H NMR ($CDCl_3$) δ: 3.59 (1H, dd), 3.51 (1H, m), 3.33 (1H, m), 3.19 (2H, d), 3.02 (1H, dd), 2.49 (1H, m), 2.07 (1H, m), 1.65 (1H, m), 1.46 (9H, s).

Intermediate 119

tert-Butyl (1aRS,7bSR)-5-{2-[N-(2,4-dimethoxybenzyl)-N-(3-dimethyl-aminopropyl)carbamoyl]benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

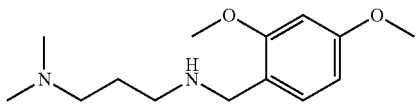


A solution of N-(2,4-dimethoxybenzyl)-N-(3-dimethylaminopropyl)amine (Intermediate 120, 0.179 g) in DCM (2 mL) was added dropwise with stirring to a cooled solution of 2-chlorosulfonylbenzoyl chloride (Intermediate 121, 0.17 g) in DCM (20 mL) at 0° C. The mixture was stirred at 0° C. for 1 hour then a solution of tert-butyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydro-cyclopropa-[c]chromene-4-carboxylate (Intermediate 122, 0.185 g) in DCM (2 mL) was added. The resultant mixture was stirred and heated at 30-35° C. overnight. After cooling, the mixture was concentrated under vacuum and the residue was purified by HPLC (C18) to give tert-butyl (1aRS,7bSR)-5-{2-[N-(2,4-dimethoxybenzyl)-N-(3-dimethylaminopropyl)carbamoyl]-benzenesulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa-[c]chromene-4-carboxylate (0.03 g) as a yellow oil.

LCMS (Method D) r/t 3.16 (M+H) 680.

Intermediate 120

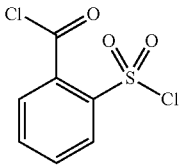
N-(2,4-Dimethoxybenzyl)-N-(3-dimethylaminopropyl)amine



A mixture of 3-dimethylaminopropylamine (3.06 g), 2,4-dimethoxybenzaldehyde (6.0 g) and sodium triacetoxyborohydride (9.54 g) in methanol (20 mL) was stirred at room temperature for 10 hours. The mixture was concentrated under vacuum and the residue was dissolved in ethyl acetate and washed with water and brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give N-(2,4-dimethoxybenzyl)-N-(3-dimethylaminopropyl)amine (7.2 g) as a brown oil which was used directly without further characterisation.

Intermediate 121

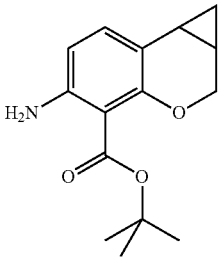
2-Chlorosulfonylbenzoyl chloride



A mixture of 1,1-dioxo-1H-1lambda*6*benzo[c][1,2]oxathiol-3-one (4.5 g) and phosphorous pentachloride (15 g) was stirred and heated at 60° C. overnight. After cooling, a mixture of ice and water was added and the solution was extracted with DCM, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give 2-chlorosulfonylbenzoyl chloride (5 g) as a yellow solid which was used without further characterisation.

Intermediate 122

tert-Butyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

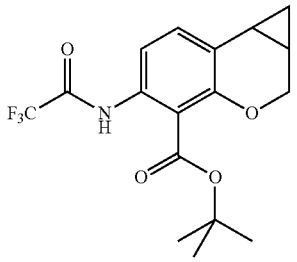


Sodium borohydride (0.32 g) was added in portions to a stirred solution of tert-butyl (1aRS,7bSR)-5-(trifluoroacetylamino)-1,1a,2,7b-tetrahydro-cyclopropa-[c]chromene-4-carboxylate (Intermediate 123, 0.5 g) in ethanol (20 mL). The resultant mixture was stirred at room temperature for 1 hour then concentrated under vacuum. The residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and petroleum ether with a gradient of 2-4% to give tert-butyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (0.2 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 7.04 (1H, d), 6.25 (1H, d), 4.57 (2H, br s), 4.32 (1H, d), 3.87 (1H, d), 1.86 (1H, m), 1.65 (1H, m), 1.60 (9H, s), 0.95 (2H, m).

Intermediate 123

tert-Butyl (1aRS,7bSR)-5-(trifluoroacetylamino)-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate

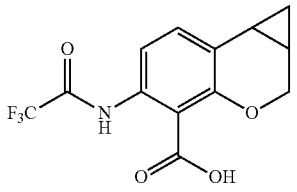


A mixture of (1aRS,7bSR)-5-(trifluoroacetylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (Intermediate 124, 0.97 g), DMAP (0.2 g), dicyclohexyl carbodiimide (1.33 g) and di-tert-butyl dicarbonate (3.51 g) in tert-butanol (20 mL) was stirred and heated at reflux for 7 hours. After cooling, the mixture was concentrated under vacuum and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and petroleum ether (2%) to give tert-butyl (1aRS,7bSR)-5-(trifluoroacetylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.5 g) as a yellow oil.

^{1}H NMR ($CDCl_3$) δ: 10.47 (1H, br s), 7.89 (1H, d), 7.34 (1H, d), 4.39 (1H, d), 3.88 (1H, d), 2.02 (1H, m), 1.77 (1H, m), 1.60 (9H, s), 1.09 (2H, m).

Intermediate 124

(1aRS,7bSR)-5-(Trifluoroacetylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid

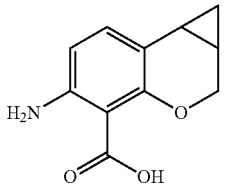


Trifluoroacetic anhydride (2.98 g) was added dropwise to a stirred, cooled solution of (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydro-cyclopropa-[c]chromene-4-carboxylic acid (Intermediate 125, 0.97 g) and triethylamine (2.39 g) in THF (20 mL). The resultant mixture was stirred at room temperature for 30 minutes. Water was added and the mixture was extracted with ethyl acetate, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and petroleum ether (2%) to give (1aRS,7bSR)-5-(trifluoroacetylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid (0.97 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 7.92 (1H, d), 7.28 (1H, d), 4.54 (1H, d), 3.94 (1H, d), 2.27 (1H, m), 2.02 (1H, m), 1.21 (1H, m), 0.95 (1H, m).

Intermediate 125

(1aRS,7bSR)-5-Amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid

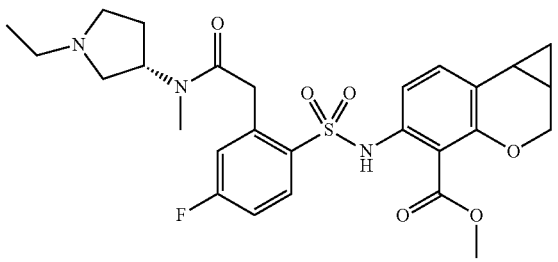


A mixture of methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 42, 1.0 g) and lithium hydroxide monohydrate (0.96 g) in dioxane (16 mL) and water (14 mL) was stirred and heated at 90° C. for 1 hour. After cooling, the mixture was concentrated under vacuum and the residue was diluted with water and neutralised to pH7 with formic acid. The mixture was then extracted with ethyl acetate, dried (Na_2SO_4) and filtered and the filtrate was evaporated to dryness to give (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydro-cyclopropa-[c]chromene-4-carboxylic acid (0.97 g) as a yellow oil.

LCMS (Method D) r/t 2.13 (M+H) 206.

Intermediate 126

Methyl (1aRS,7bSR)-5-(2-{[N—((S)-1-ethylpyrrolidin-3-yl)-N-methyl-carbamoyl]-methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate



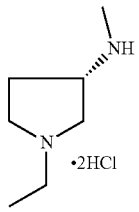
EDAC (0.058 g) was added to a stirred solution of methyl (1aRS,7bSR)-5-(2-carboxymethyl-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 83, 0.109 g) in DCM (3 mL) and the mixture was stirred at room temperature for 10 minutes. A

solution of N—((S)-1-ethylpyrrolidin-3-yl)-N-methylamine dihydrochloride (Intermediate 127, 0.102 g) and triethylamine (0.151 g) in DCM (3 mL) was added and the mixture stirred for 17 hours. The mixture was evaporated in vacuo and the residue was dissolved in dioxane (4 mL) and the mixture was heated at 75° C. for 20 hours. After cooling, the mixture was diluted with DCM and water and filtered through a phase separator. The filtrate was evaporated in vacuo and the residue was combined with an identical reaction carried out earlier. The material was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-50% to give methyl (1aRS,7bSR)-5-(2-{[((S)-1-ethylpyrrolidin-3-yl)methylcarbamoyl]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (0.48 g) as a light brown foam.

LCMS (Method E) r/t 2.65 (M+H) 546.

Intermediate 127

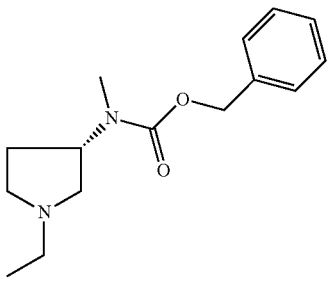
N—((S)-1-Ethylpyrrolidin-3-yl)-N-methylamine dihydrochloride



A mixture of benzyl N—((S)-1-ethylpyrrolidin-3-yl)-N-methylcarbamate (Intermediate 128, 0.682 g) and 10% palladium on carbon (0.10 g) in ethanol (20 mL) was stirred at room temperature under an atmosphere of hydrogen for 3 hours. The mixture was filtered, and concentrated hydrochloric acid (2 mL) was added. The solution was evaporated in vacuo then redissolved in a mixture of toluene and ethanol then re-evaporated to give N—((S)-1-ethylpyrrolidin-3-yl)-N-methylamine dihydrochloride (0.531 g) as a light coloured, viscous oil which was used without further characterisation.

Intermediate 128

Benzyl N—((S)-1-ethylpyrrolidin-3-yl)-N-methylcarbamate

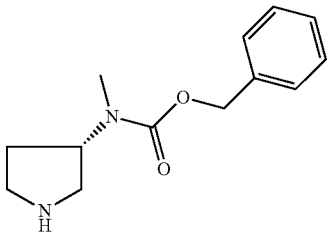


A mixture of benzyl N-methyl-(S)-pyrrolidin-3-ylcarbamate (Intermediate 129, 1.28 g), iodoethane (0.853 g), and potassium carbonate (1.51 g) in acetonitrile (12 mL) was stirred at room temperature for 4 hours. The mixture was evaporated in vacuo and the residue was basified with 5M sodium hydroxide and filtered through a phase separator. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-30% to give benzyl N—((S)-1-ethylpyrrolidin-3-yl)-N-methylcarbamate (0.686 g) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ: 7.35 (5H, m), 5.13 (2H, s), 4.84 (1H, br, s), 2.91 (3H, s), 2.30-2.82 (6H, m), 2.12 (1H, br, m), 1.79 (1H, m), 1.10 (3H, t).

Intermediate 129

Benzyl N-methyl-(S)-pyrrolidin-3-ylcarbamate

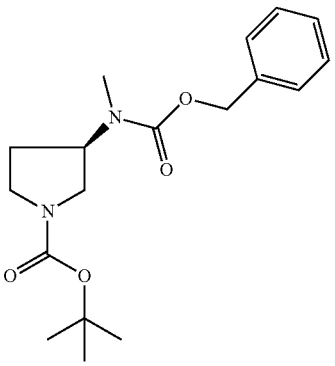


A solution of tert-butyl (S)-3-(N-benzyloxycarbonyl-N-methylamino)pyrrolidine-1-carboxylate (Intermediate 130, 1.81 g) in trifluoroacetic acid (8 mL) and DCM (8 mL) was left to stand at room temperature for 30 minutes. The resultant mixture was concentrated in vacuo and the residue was dissolved in DCM and brine, basified with 2M sodium hydroxide and filtered through a phase separator. The filtrate was concentrated in vacuo to give benzyl N-methyl-(S)-pyrrolidin-3-ylcarbamate (1.46 g) as a light coloured oil.

^{1}H NMR ($CDCl_3$) δ: 7.35 (5H, m), 5.14 (2H, s), 4.68 (1H, br, m), 3.08 (2H, m), 2.88 (3H, s), 2.76-2.95 (3H, m), 2.01 (1H, m), 1.75 (1H, m).

Intermediate 130

tert-Butyl (S)-3-(N-benzyloxycarbonyl-N-methylamino)pyrrolidine-1-carboxylate



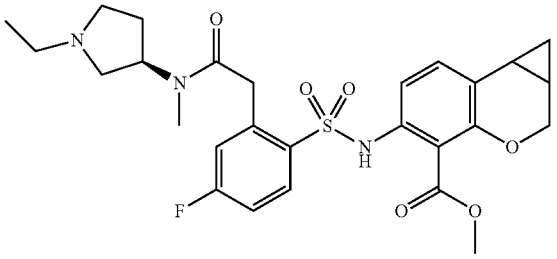
Sodium hydride (60% oil dispersion, 0.32 g) was added to a stirred solution of tert-butyl (S)-3-benzyloxycarbonylaminopyrrolidine-1-carboxylate (prepared according to Cheng et al, WO2007 142585, 1.73 g) in THF (20 mL) and the mixture was stirred for 15 minutes. Iodomethane (1.85 g) was added

and the mixture was stirred at room temperature for 1 hour. Methanol was carefully added to destroy the excess sodium hydride then ethyl acetate and water were added and the organic layer was washed with brine, dried (Na_2SO_4), filtered. The filtrate was concentrated in vacuo to give tert-butyl (S)-3-(N-benzyloxycarbonyl-N-methylamino)pyrrolidine-1-carboxylate (1.66 g) as a pale coloured oil.

^{1}H NMR ($CDCl_3$) δ: 7.36 (5H, m), 5.15 (2H, s), 4.79 (1H, br, s), 3.54 (2H, br, m), 3.11-3.38 (2H, br, m), 2.86 (3H, s), 1.98 (2H, m), 1.46 (9H, s).

Intermediate 131

Methyl (1aRS,7bSR)-5-(2-{[N—((R)-1-ethylpyrrolidin-3-yl)-N-methyl-carbamoyl]methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

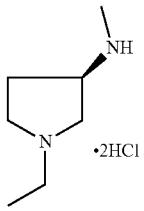


Prepared by proceeding in a similar manner to Intermediate 126, starting from methyl (1aRS,7bSR)-5-(2-carboxymethyl-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 83) and N—((R)-1-ethylpyrrolidin-3-yl)-N-methylamine dihydrochloride (Intermediate 132) as a light brown foam.

LCMS (Method E) r/t 2.63 (M+H) 546

Intermediate 132

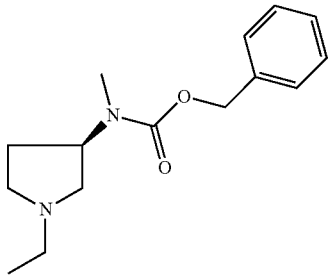
N—((R)-1-Ethylpyrrolidin-3-yl)-N-methylamine dihydrochloride



Prepared by proceeding in a similar manner to Intermediate 127, starting from benzyl N—((R)-1-ethylpyrrolidin-3-yl)-N-methylcarbamate (Intermediate 133) as a light coloured viscous oil, which was used without further characterization.

Intermediate 133

Benzyl N—((R)-1-ethylpyrrolidin-3-yl)-N-methyl-carbamate

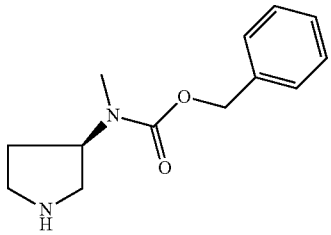


Prepared by proceeding in a similar manner to Intermediate 128, starting from benzyl N-methyl-(R)-pyrrolidin-3-yl-carbamate (including bridged or fused rings, and Intermediate 134) and iodoethane, as a light coloured oil.

^{1}H NMR ($CDCl_3$) δ: 7.35 (5H, m), 5.13 (2H, s), 4.84 (1H, br, s), 2.91 (3H, s), 2.30-2.87 (6H, m), 2.12 (1H, br, m), 1.80 (1H, m), 1.10 (3H, t).

Intermediate 134

Benzyl N-methyl-(R)-pyrrolidin-3-ylcarbamate

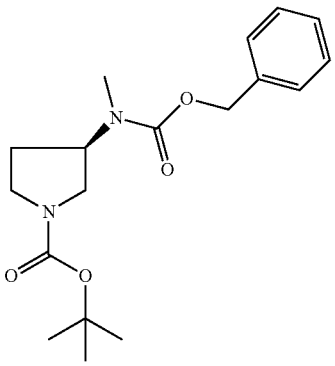


Prepared by proceeding in a similar manner to Intermediate 129, starting from tert-butyl (R)-3-(N-benzyloxycarbonyl-N-methylamino)-pyrrolidine-1-carboxylate (Intermediate 135) as a pale coloured oil.

^{1}H NMR ($CDCl_3$) δ: 7.35 (5H, m), 5.14 (2H, s), 4.79 (1H, br, s), 3.08 (2H, m), 2.88 (3H, s), 2.76-2.95 (3H, m), 2.01 (1H, m), 1.75 (1H, m).

Intermediate 135

tert-Butyl (R)-3-(N-benzyloxycarbonyl-N-methylamino)pyrrolidine-1-carboxylate

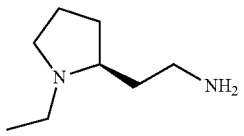


Prepared by proceeding in a similar manner to Intermediate 130, starting from tert-butyl (R)-3-benzyloxycarbonylaminopyrrolidine-1-carboxylate (prepared according to Zhou et al, US 2008 0293771) and iodomethane, as a pale coloured oil.

^{1}H NMR ($CDCl_3$) δ: 7.35 (5H, m), 5.15 (2H, s), 4.69 (1H, br, s), 3.54 (2H, br, m), 3.11-3.38 (2H, br, m), 2.86 (3H, s), 1.98 (2H, m), 1.46 (9H, s).

Intermediate 136

2((S)-1-Ethylpyrrolidin-2-yl)ethylamine

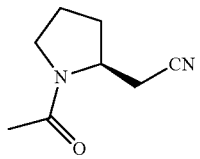


((S)-1-Acetylpyrrolidin-2-yl)acetonitrile (Intermediate 137, 1.0 g) was added portionwise to a stirred, cooled solution of lithium aluminium hydride (0.36 g) in THF (30 mL) under an atmosphere of nitrogen while maintaining the temperature at 0° C. The mixture was allowed to warm to room temperature then heated at reflux for 2 hours. After cooling, ethanol (4 mL) was added dropwise and the resultant solid was filtered off. The filtrate was evaporated to dryness to give 2((S)-1-ethylpyrrolidin-2-yl)ethylamine (0.6 g) as a colourless oil.

^{1}H NMR (D_2O) δ: 3.59 (1H, m), 3.37 (2H, m), 3.01 (4H, m), 2.24 (2H, m), 1.98 (3H, m), 1.65 (1H, m), 1.21 (3H, t).

Intermediate 137

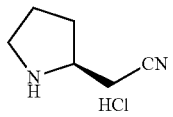
((S)-1-Acetylpyrrolidin-2-yl)acetonitrile



Acetyl chloride (8.6 g) was added dropwise to a stirred, cooled solution of ((S)-pyrrolidin-2-yl)acetonitrile hydrochloride (Intermediate 138, 8.0 g) and triethylamine (16.5 g) in DCM (80 mL) while maintaining the temperature at 0° C. The resultant solution was stirred at 0° C. for 30 minutes. Water was added and the layers were separated. The aqueous layer was further extracted with DCM and the combined organic layers were washed with brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by HPLC (C18) to give ((S)-1-acetylpyrrolidin-2-yl)acetonitrile (5.0 g) as a light yellow oil which was used directly without further characterisation.

Intermediate 138

((S)-Pyrrolidin-2-yl)acetonitrile hydrochloride

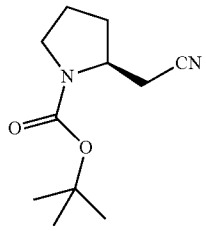


A solution of tert-butyl (S)-2-cyanomethylpyrrolidine-1-carboxylate (Intermediate 139, 13.0 g) in methanol (130 mL) and concentrated hydrochloric acid (13 mL) was stirred and heated at 40° C. overnight. After cooling, the mixture was concentrated under vacuum and the residue was diluted with toluene and reconcentrated. Ethanol (20 mL) was added and the resultant solid was collected by filtration and washed with hexane to give ((S)-pyrrolidin-2-yl)acetonitrile hydrochloride (8.0 g) as a white solid.

LCMS (Method D) r/t 0.50 (M+H) 111.

Intermediate 139

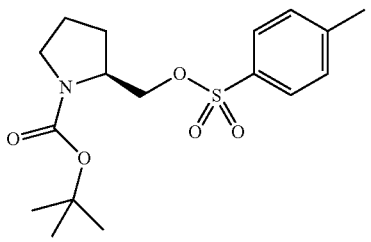
tert-Butyl (S)-2-cyanomethylpyrrolidine-1-carboxylate



Sodium cyanide (8.2 g) was added to a solution of tert-butyl (S)-2-(4-methylbenzenesulfonyloxymethyl)pyrrolidine-1-carboxylate (Intermediate 140, 29.6 g) in DMSO (300 mL) and the resultant mixture was stirred and heated at 90° C. for 5.5 hours. After cooling, the mixture was treated with saturated aqueous iron (II) sulphate solution and the mixture was stirred for a further 5 hours then extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and petroleum ether (5%) to give tert-butyl (S)-2-cyanomethylpyrrolidine-1-carboxylate (13.0 g) as a light yellow oil which was used without further characterisation.

Intermediate 140

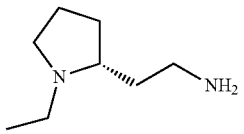
tert-Butyl (S)-2-(4-methylbenzenesulfonyloxymethyl)pyrrolidine-1-carboxylate



4-Methylbenzenesulfonyl chloride (22.7 g) was added portionwise to a stirred, cooled solution of tert-butyl (S)-2-hydroxyoxymethylpyrrolidine-1-carboxylate (20.0 g) in pyridine (70 mL) while maintaining the temperature at 0° C. The resultant mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum and the residue was dissolved in DCM and washed with saturated aqueous sodium bicarbonate solution and brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give tert-butyl (S)-2-(4-methylbenzenesulfonyl-oxymethyl)pyrrolidine-1-carboxylate (34 g) as a yellow oil which was used without further characterisation.

Intermediate 141

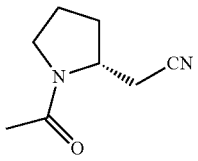
2-((R)-1-Ethylpyrrolidin-2-yl)ethylamine



Prepared by proceeding in a similar manner to Intermediate 136, starting from ((S)-1-acetylpyrrolidin-2-yl)acetonitrile (Intermediate 142) and used without further characterisation.

Intermediate 142

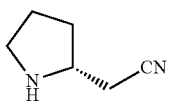
((R)-1-Acetylpyrrolidin-2-yl)acetonitrile



Prepared by proceeding in a similar manner to Intermediate 137, starting from ((R)-pyrrolidin-2-yl)acetonitrile hydrochloride (Intermediate 143) and used without further characterisation.

Intermediate 143

((R)-Pyrrolidin-2-yl)acetonitrile hydrochloride

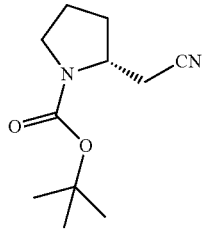


HCl

Prepared by proceeding in a similar manner to Intermediate 138, starting from tert-butyl (R)-2-cyanomethylpyrrolidine-1-carboxylate (Intermediate 144) and used without further characterisation.

Intermediate 144

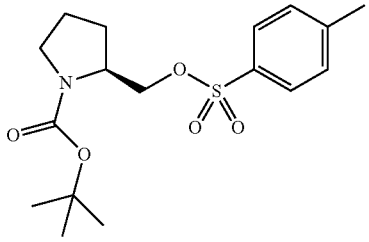
tert-Butyl (R)-2-cyanomethylpyrrolidine-1-carboxylate



Prepared by proceeding in a similar manner to Intermediate 139, starting from tert-butyl (R)-2-(4-methylbenzenesulfonyloxymethyl)pyrrolidine-1-carboxylate (Intermediate 145) and used without further characterisation.

Intermediate 145

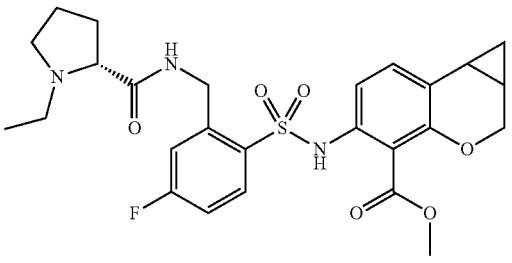
tert-Butyl (R)-2-(4-methylbenzenesulfonyloxymethyl)pyrrolidine-1-carboxylate



Prepared by proceeding in a similar manner to Intermediate 140, starting from tert-butyl (R)-2-hydroxymethylpyrrolidine-1-carboxylate and used without further characterisation.

Intermediate 146

Methyl (1aRS,7bSR)-5-(2-{[((R)-1-ethylpyrrolidine-2-yl)carbonylamino]-methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

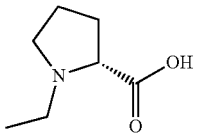


Prepared by proceeding in a similar manner to Intermediate 101, starting from methyl (1aRS,7bSR)-5-(2-aminomethyl-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 102) and (R)-1-ethylpyrrolidine-2-carboxylic acid (Intermediate 147) as a solid.

LCMS (Method B) r/t 2.37 (M+H) 532

Intermediate 147

(R)-1-Ethyl-pyrrolidine-2-carboxylic acid

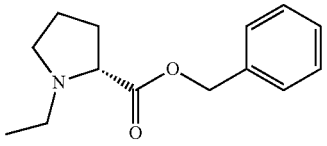


Prepared by proceeding in a similar manner to Intermediate 106, starting from tert-butyl (R)-1-ethylpyrrolidine-2-carboxylate (Intermediate 148) as a solid.

^{1}H NMR ($CDCl_3$) δ: 3.99 (1H, m), 3.76 (1H, dd), 3.37-3.23 (1H, m), 3.21-3.08 (1H, m), 2.84 (1H, dt), 2.45-2.21 (2H, m), 2.07-1.94 (2H, m), 1.39 (3H, t).

Intermediate 148

Benzyl (R)-1-ethylpyrrolidine-2-carboxylate

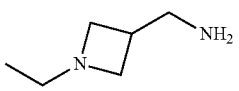


Prepared by proceeding in a similar manner to Intermediate 107, starting from benzyl (R)-pyrrolidine-2-carboxylate as a colourless oil.

^{1}H NMR ($CDCl_3$) δ: 7.34 (5H, m), 5.17 (2H, s), 3.19 (2H, m), 2.75 (1H, m), 2.45 (1H, m), 2.33 (1H, m), 2.12 (1H, m), 1.93 (2H, m), 1.81 (1H, m), 1.09 (3H, t).

Intermediate 149

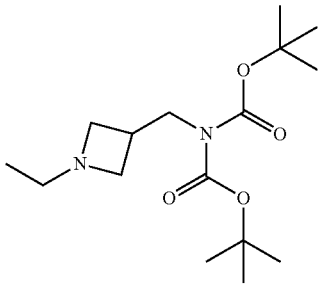
(1-Ethylazetidin-3-yl)methylamine



A solution of 3-[bis-(tert-butoxycarbonylamino)methyl]-1-ethylazetidine (Intermediate 150, 0.83 g) in a mixture of methanol (6 mL) and concentrated hydrochloric acid (1 mL) was stirred and heated at 50° C. for 3 hours. After cooling, the mixture was concentrated under vacuum and the residue was dissolved in isopropanol and treated with potassium carbonate (3 g). The mixture was stirred at room temperature for 48 hours, then the solid was filtered off and the filtrate was evaporated to dryness to give (1-ethylazetidin-3-yl)methylamine (0.18 g) as a light sticky gum which was used without further characterisation.

Intermediate 150

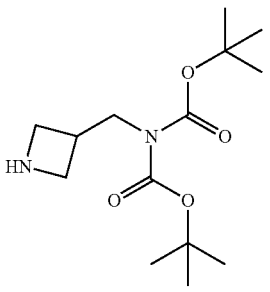
3-[bis-(tert-Butoxycarbonylamino)methyl]-1-ethylazetidine



A mixture of acetaldehyde (1.5 g) and 3-[bis-(tert-butoxycarbonyl-amino)methyl]azetidine (Intermediate 151, 1.0 g) in ethanol (20 mL) was stirred at room temperature for 30 minutes and then 10% palladium on carbon (0.3 g) was added. The mixture was stirred under an atmosphere of hydrogen overnight. The solid was filtered off and the filtrate was evaporated to dryness. The residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM (10%) to give 3-[bis-(tert-butoxycarbonylamino)methyl]-1-ethylazetidine (0.83 g) as a colourless liquid, which was used without further characterization.

Intermediate 151

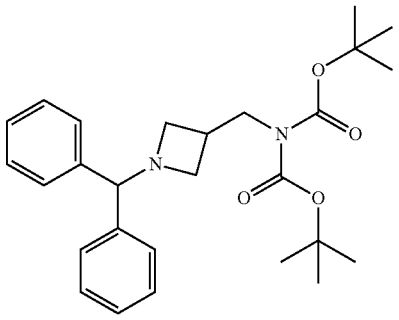
3-[bis-(tert-Butoxycarbonylamino)methyl]azetidine



A mixture of 3-[bis-(tert-butoxycarbonylamino)methyl]-1-(diphenylmethyl)azetidine (Intermediate 152, 6.4 g) and 10% palladium on carbon (3 g) in ethanol (100 mL) and acetic acid (2 mL) was stirred under an atmosphere of hydrogen overnight. The solid was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in ethyl acetate and washed with saturated aqueous sodium carbonate, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM (10%) to give 3-[bis-(tert-butoxycarbonylamino)methyl]azetidine (4.0 g) as a colourless liquid, which was used without further characterisation.

Intermediate 152

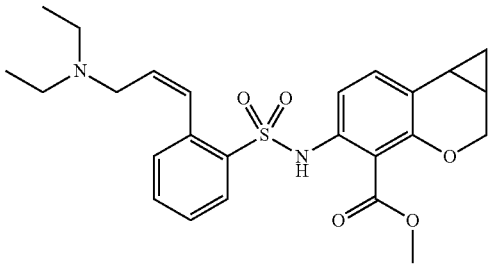
3-[bis-(tert-Butoxycarbonylamino)methyl]-1-(diphenylmethyl)-azetidine



Di-tert-butyl dicarbonate (22 g) was added to a solution of 1-(diphenylmethyl)azetidin-3-ylmethylamine (5 g), DMAP (0.5 g) and triethylamine (12 g) in THF (150 mL) and the resultant solution was stirred and heated at 60° C. for 5 hours. After cooling, the mixture was added to brine solution and extracted with ethyl acetate, washed with brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and petroleum ether (10%) to give 3-[bis-(tert-butoxycarbonylamino)methyl]-1-(diphenylmethyl)azetidine (6.4 g) as a white solid, which was used without further characterisation.

Intermediate 153

Methyl (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

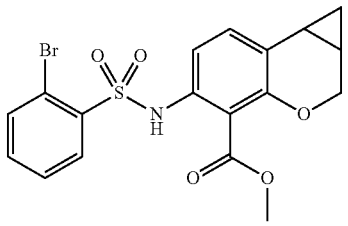


A mixture of methyl (1aRS,7bSR)-5-(2-bromobenzenesulfonylamino)-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (Intermeidate 154, 0.612 g), N,N-diethyl-N—((Z)-1-tributylstannanylprop-1-en-3-yl)amine (Intermediate 11, 1.13 g), tri-tert-butylphosphonium tetrafluoroborate (0.041 g), tris-(dibenzylideneacetone)dipalladium (0.064 g) in dioxane (12 mL) and DMSO (0.4 mL) was degassed and purged with nitrogen then heated at 100° C. for 1.5 hours. After cooling, the mixture was diluted with brine and extracted with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-15% to give methyl (1aRS,7bSR)-5-[2-((Z)-3-diethylamino-prop-1-enyl)benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.495 g) as a solid.

^{1}H NMR ($CDCl_3$) δ: 8.06 (1H, dd), 7.52 (1H, m), 7.40 (1H, m), 7.30 (1H, m), 7.14 (1H, d), 7.01 (1H, m), 6.86 (1H, d), 6.02 (1H, m), 4.33 (1H, d), 3.84 (3H, s), 3.77 (1H, d), 3.12 (2H, br s), 2.51 (4H, br s), 1.87 (1H, m), 1.70 (1H, m), 1.05-0.85 (8H, m).

Intermediate 154

Methyl (1aRS,7bSR)-5-(2-bromobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

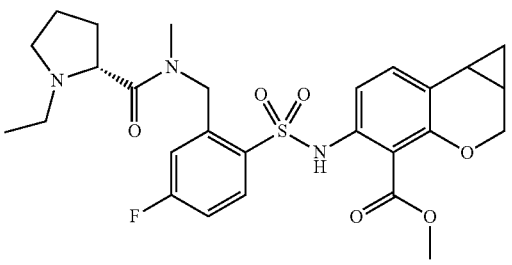


2-Bromobenzenesulfonyl chloride (0.559 g) was added to a solution of methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 42, 0.40 g) in DCM (12 mL) and pyridine (4 mL) and the resultant mixture was stirred at room temperature for 1 hour. The mixture was evaporated to dryness and the residue was dissolved in DCM and washed with 2N HCl, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-35% to give methyl (1aRS,7bSR)-5-(2-bromobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.612 g) as a solid.

^{1}H NMR ($CDCl_3$) δ: 9.85 (1H, s), 7.89 (1H, dd), 7.85 (1H, dd), 7.57-7.49 (2H, m), 7.26 (1H, d), 6.64 (1H, d), 4.27 (1H, d), 3.72 (1H, d), 3.66 (3H, s), 2.05-1.95 (1H, m), 1.86-1.76 (1H, m), 1.08-0.98 (1H, m), 0.84-0.76 (1H, m).

Intermediate 155

Methyl (1aRS,7bSR)-5-(2-{N—[((R)-1-ethylpyrrolidine-2-yl)carbonyl]-N-methylaminomethyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate



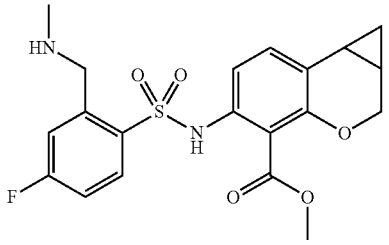
HATU (0.136 g) was added to a mixture of methyl (1aRS,7bSR)-5-(4-fluoro-2-methylaminomethylbenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 156, 0.150 g), (R)-1-ethylpyrrolidine-2-carboxylic acid (Intermediate 147, 0.061 g) and N,N-diisopropyl-N-ethylamine (0.124 mL) in DMF (5

mL) and the mixture was stirred for 3 days at room temperature. The volatiles were removed in vacuo and the residue was extracted with ethyl acetate (50 mL). The organic layer was washed with water (50 mL), brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of methanol and DCM with a gradient of 0-10% to give methyl (1aRS,7bSR)-5-(2-{N—[((R)-1-ethylpyrrolidine-2-yl)carbonyl]methylamino]-methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.177 g) as a solid.

LCMS (Method F) r/t 2.33 (M+H) 546.

Intermediate 156

Methyl (1aRS,7bSR)-5-(4-fluoro-2-methylaminomethylbenzenesulfonyl-amino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

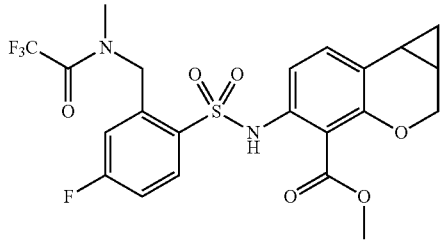


A solution of potassium carbonate (0.345 g) in water (2 mL) was added to a solution of methyl (1aRS,7bSR)-5-(4-fluoro-2-[N-methyl-N-(2,2,2-trifluoroacetyl)-aminomethyl]-benzenesulfonyl-amino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 157, 0.257 g) in methanol (12 mL) and the mixture was heated at 45° C. for 3 hours. After cooling, the volatiles were removed in vacuo and the residue was treated with water (30 mL) and saturated with sodium chloride and extracted with ethyl acetate (50 mL). The organic layer was dried (Na_2SO_4) and filtered and the filtrate was evaporated to dryness to give methyl (1aRS,7bSR)-5-(4-fluoro-2-methylaminomethylbenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.156 g) as a solid.

LCMS (Method B) r/t 2.14 (M+H) 421.

Intermediate 157

Methyl (1aRS,7bSR)-5-(4-fluoro-2-[N-methyl-N-(2,2,2-trifluoroacetyl)-aminomethyl]benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

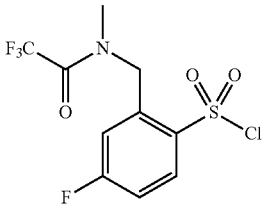


A mixture of 4-fluoro-2-[N-methyl-N-(2,2,2-trifluoroacetyl)aminomethyl]benzenesulfonyl chloride (Intermediate 158, 0.182 g) was added to a solution of methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 42, 0.100 g) in DCM (3 mL) and pyridine (1 mL) and the resultant mixture was stirred at room temperature for 1 hour. The mixture was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-40% to give methyl (1aRS,7bSR)-5-(4-fluoro-2-[N-methyl-N-(2,2,2-trifluoroacetyl)aminomethyl]benzenesulfonyl-amino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.257 g) as a solid.

LCMS (Method F) r/t 3.77 (M+H) 517.

Intermediate 158

4-Fluoro-2-[N-methyl-N-(2,2,2-trifluoroacetyl)aminomethyl]benzene-sulfonyl chloride

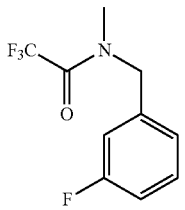


A solution of 3-fluoro-N-methyl-N-(trifluoroacetyl)benzylamine (Intermediate 159, 0.497 g) in DCE (0.5 mL) was added to stirred, cooled chlorosulfonic acid (3 mL). The mixture was allowed to come up to room temperature and then heated at 70° C. for 3 hours. After cooling, the mixture was added carefully to a mixture of ice and water, then extracted with ethyl acetate, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and pentane with a gradient of 2.5-10% to give 4-fluoro-2-[N-methyl-N-(2,2,2-trifluoroacetyl)aminomethyl]-benzenesulfonyl chloride (0.21 g) as a clear oil.

^1H NMR ($CDCl_3$) δ: 8.20 (1H, m), 7.24 (1H, m), 7.01 (1H, d), 5.21 (2H, s), 3.24 (2H, s), 3.13 (1H, s).

Intermediate 159

3-Fluoro-N-methyl-N-(trifluoroacetyl)benzylamine



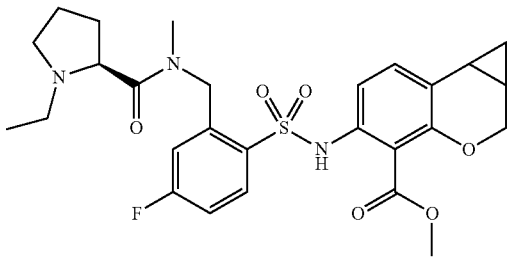
A solution of 3-fluoro-N-(trifluoroacetyl)benzylamine (Intermediate 105, 0.508 g) in THF (5 mL) was added to a stirred suspension of sodium hydride (60% oil dispersion, 0.096 g) in THF (5 mL). The resultant mixture was stirred at room temperature for 30 minutes. Iodomethane (0.653 g) was added and the mixture was stirred at room temperature overnight. The mixture was poured into water and extracted with ethyl acetate, washed with water, dried ($MgSO_4$) and filtered.

The filtrate was evaporated to dryness to give 3-fluoro-N-methyl-N-(trifluoroacetyl)benzylamine (0.497 g) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 7.34 (1H, m), 7.10-6.90 (3H, m), 4.63 (2H, s), 3.07 (2H, q), 2.94 (1H, s).

Intermediate 160

Methyl (1aRS,7bSR)-5-(2-[N—((S)-1-ethylpyrrolidine-2-yl)carbonyl-N-methylaminomethyl]-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

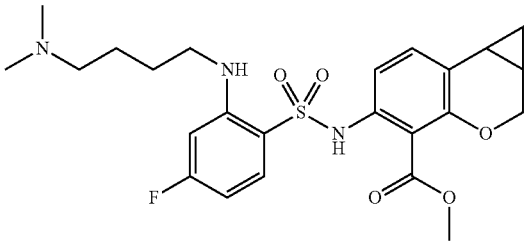


Prepared by proceeding in a similar manner to Intermediate 155, starting from methyl (1aRS,7bSR)-5-(4-fluoro-2-methylaminomethylbenzenesulfonylamino)-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (intermediate 156) and (S)-1-ethylpyrrolidine-2-carboxylic acid (Intermediate 106) as a solid.

LCMS (Method B) r/t 2.47 (M+H) 546.

Intermediate 161

Methyl (1aRS,7bSR)-5-[2-(4-dimethylaminobutylamino)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

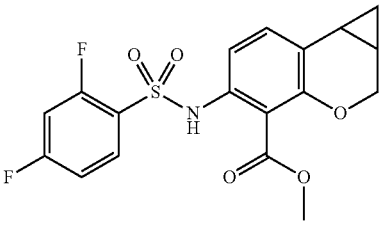


A solution of methyl (1aRS,7bSR)-5-(2,4-difluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydro-cyclopropa[c] chromene-4-carboxylate (Intermediate 162, 0.675 g) and N,N-dimethylbutane-diamine (0.496 g) in dioxane (20 mL) was stirred and heated at 80° C. for 17 hours then left at room temperature for 3 days. The solution was diluted with ethyl acetate, washed with potassium carbonate solution and water then dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-40% to give methyl (1aRS,7bSR)-5-[2-(4-dimethyl-aminobutylamino)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (0.499 g) as a colourless gum.

^{1}H NMR ($CDCl_3$) δ: 7.51 (1H, dd), 7.26 (1H, d), 7.12 (1H, d), 6.29 (2H, m), 6.00 (1H, br, s), 4.31 (1H, d), 3.75 (1H, d), 3.50 (3H, s), 3.01 (2H, m), 2.25 (6H, s), 2.11 (2H, t), 1.94 (1H, m), 1.73 (1H, m), 1.58 (4H, m), 1.03 (2H, m).

Intermediate 162

Methyl (1aRS,7bSR)-5-(2,4-difluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c] chromene-4-carboxylate

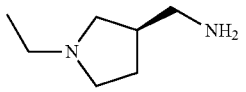


2,4-Difluorobenzenesulphonyl chloride (0.468 g) was added to a solution of methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylater (Intermediate 42, 0.438 g) in pyridine (2 mL) and DCM (4 mL) and the solution was left at room temperature for 2 hours. The mixture was diluted with DCM, washed with 2M hydrochloric acid, dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-30% to give methyl (1aRS,7bSR)-5-(2,4-difluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.761 g) as a light coloured gum.

^{1}H NMR ($CDCl_3$) δ: 8.90 (1H, br, s), 7.82 (1H, m), 7.22 (1H, d), 7.13 (1H, d), 6.88 (2H, m), 4.32 (1H, d), 3.89 (3H, s), 3.79 (1H, d), 1.90 (1H, m), 1.71 (1H, m), 1.01 (2H, m).

Intermediate 163

((R)-1-Ethylpyrrolidin-3-ylmethyl)amine

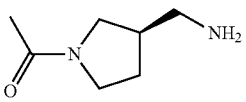


Lithium aluminium hydride was added to a stirred solution of ((R)-1-acetylpyrrolidin-3-ylmethyl)amine (Intermediate 164, 1.5 g) in THF (50 mL) and the resulting mixture was stirred and heated at reflux for 2 hours. After cooling, ethanol was slowly added and the mixture was concentrated under vacuum. The residue was diluted with DCM and the solid was filtered off. The filtrate was evaporated to dryness to give ((R)-1-ethylpyrrolidin-3-ylmethyl)amine (0.9 g) as a yellow solid.

LCMS (Method D) r/t 0.396 (M+H) 129.

Intermediate 164

((R)-1-Acetylpyrrolidin-3-ylmethyl)amine

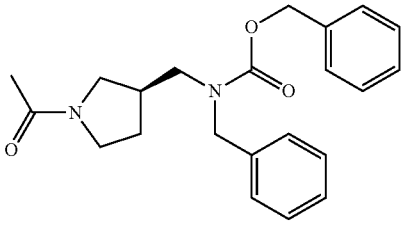


A mixture of benzyl N—((S)-1-acetylpyrrolidin-3-ylmethyl)-N-benzylcarbamate (Intermediate 165, 4.2 g) and palladium hydroxide on carbon (0.4 g) in methanol (42 mL) was stirred under an atmosphere of hydrogen at 60° C. for 48 hours. The mixture was filtered and the filtrate was evaporated to dryness to give ((R)-1-acetylpyrrolidin-3-ylmethyl)amine (1.5 g) as a light yellow oil.

LCMS (Method D) r/t 0.49 (M+H) 143.

Intermediate 165

Benzyl N—((S)-1-acetylpyrrolidin-3-ylmethyl)-N-benzylcarbamate

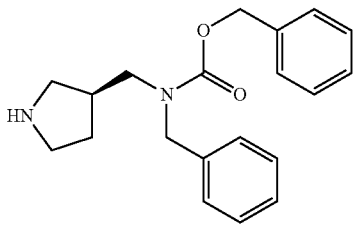


Acetyl chloride (2.86 g) was added to a stirred solution of benzyl N—((S)-pyrrolidin-3-ylmethyl)-N-benzylcarbamate (Intermediate 166, 5.9 g) and triethylamine (3.68 g) in DCM (80 mL) with ice cooling. The resultant mixture was stirred at room temperature for 2 hours then concentrated under vacuum. The residue was treated with saturated aqueous sodium bicarbonate and extracted with ethyl acetate, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with ethyl acetate to give benzyl N—((S)-1-acetylpyrrolidin-3-ylmethyl)-N-benzylcarbamate (4.2 g) as a yellow oil.

LCMS (Method D) r/t 1.65 (M+H) 367.

Intermediate 166

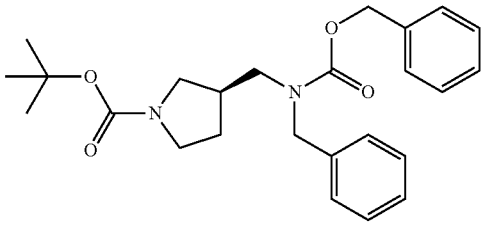
Benzyl N—((S)-pyrrolidin-3-ylmethyl)-N-benzylcarbamate



tert-Butyl (S)-3-[N-benzyl-N-(benzyloxycarbonyl)aminomethyl]pyrrolidine-1-carboxylate (Intermediate 167, 11 g) was added dropwise to a solution of acetyl chloride (15 g) in methanol (50 mL) and the resultant mixture was stirred at room temperature overnight. The mixture was concentrated under vacuum and the residue was purified by HPLC (C18) to give benzyl N—((S)-pyrrolidin-3-ylmethyl)-N-benzylcarbamate (8.0 g) as an off white solid which was used without further characterisation.

Intermediate 167

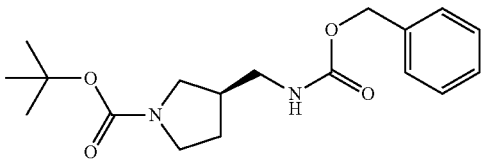
tert-Butyl (S)-3-[N-benzyl-N-(benzyloxycarbonyl) aminomethyl]-pyrrolidine-1-carboxylate



A solution of tert-butyl (R)-3-(N-benzyloxycarbonyl)aminomethylpyrrolidine-1-carboxylate (Intermediate 168, 19 g) in DMF (90 mL) was added dropwise to a suspension of sodium hydride (60%, 4.55 g) in DMF (100 mL). After stirring for 30 minutes, benzyl bromide (11.7 g) was added dropwise. The resultant mixture was stirred and heated at 70° C. overnight. After cooling, saturated aqueous sodium bicarbonate was added and the mixture was extracted with eithyl acetate, dried (Na_2SO_4) and filtered. The filtrate was purified by chromatography on silica, eluting with a mixture of ethyl acetate and petroleum ether (10%) to give tert-butyl (S)-3-[N-benzyl-N-(benzyloxycarbonyl)aminomethyl]-pyrrolidine-1-carboxylate (11.0 g) as a light yellow oil, which was used without further characterisation.

Intermediate 168

tert-Butyl (R)-3-(N-benzyloxycarbonyl)aminomethylpyrrolidine-1-carboxylate

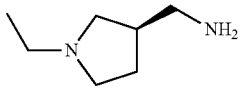


Benzyl chloroformate (14.1 g) was added dropwise to a cooled solution of tert-butyl (R)-3-aminomethylpyrrolidine-1-carboxylate (15 g) in THF (150 mL) while maintaining the temperature below 0° C. On completion of the addition, triethylamine (15.2 g) was added dropwise. The resultant mixture was stirred at −5° C. for 30 minutes then at room temperature overnight. Brine was added and the mixture was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give tert-butyl (R)-3-(N-benzyloxycarbonyl)aminometh-

ylpyrrolidine-1-carboxylate (23 g) as a colourless sticky gum, which was used without further characterisation.

Intermediate 169

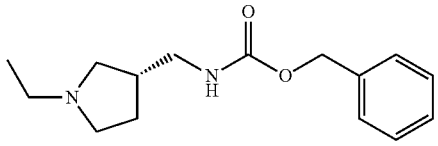
((S)-1-Ethylpyrrolidin-3-yl)methylamine



Palladium on carbon (10%, 0.3 g) was added to a solution of benzyl N—((S)-1-ethylpyrrolidin-3-ylmethyl)carbamate (Intermediate 170, 1.8 g) in methanol (20 mL) and the resultant mixture was stirred under an atmosphere of hydrogen for 24 hours. The mixture was filtered and the filtrate was evaporated to dryness to give ((S)-1-ethylpyrrolidin-3-yl)methylamine (0.8 g) as a colourless oil, which was used without further characterisation.

Intermediate 170

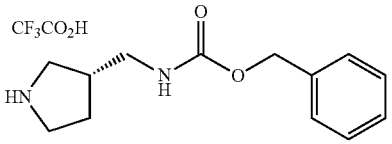
Benzyl N—((S)-1-ethylpyrrolidin-3-ylmethyl)carbamate



Iodoethane (4.1 g) was added to a cooled mixture of benzyl N—((R)-pyrrolidin-3-ylmethyl)carbamate trifluoroacetate salt (Intermediate 171, 7.6 g) and potassium carbonate (12.2 g) in DMF (10 mL) while maintaining the temperature at 0° C. The mixture was then stirred at room temperature for 4 hours. Water was added and the mixture was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give benzyl N—((S)-1-ethylpyrrolidin-3-ylmethyl)carbamate (1.8 g) as a colourless oil, which was used without further characterisation.

Intermediate 171

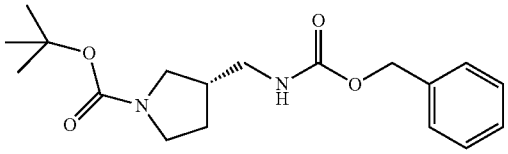
Benzyl N—((R)-pyrrolidin-3-ylmethyl)carbamate trifluoroacetate salt



A mixture of tert-butyl (S)-3-(N-benzyloxycarbonyl)aminomethylpyrrolidine-1-carboxylate (Intermediate 172, 8.0 g) in trifluoroacetic acid (10 mL) was stirred at room temperature for 5 hours. The mixture was concentrated under vacuum to give crude benzyl N—((R)-pyrrolidin-3-ylmethyl)carbamate trifluoroacetate salt (7.6 g) as a light brown oil which was used without further purification or characterisation.

Intermediate 172

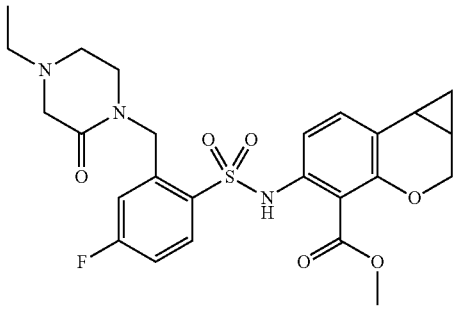
tert-Butyl (S)-3-(N-benzyloxycarbonyl)aminomethylpyrrolidine-1-carboxylate



Prepared by proceeding in a similar manner to Intermediate 168, starting form tert-butyl (S)-3-aminomethylpyrrolidine-1-carboxylate and used without further characterisation.

Intermediate 173

Methyl (1aRS,7bSR)-5-[2-(4-Ethyl-2-oxopiperazin-1-ylmethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate



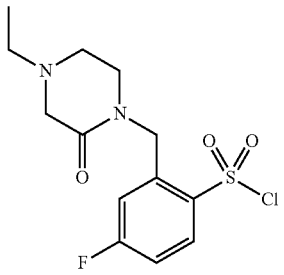
A solution of 2-(4-ethyl-2-oxopiperazin-1-ylmethyl)-4-fluorobenzenesulfonyl chloride (Intermediate 174, 0.368 g) and methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (Intermediate 42, 0.219 g) in pyridine (3 mL) and DCM (3 mL) was left to stand at room temperature for 17 hours. The mixture was evaporated in vacuo and the residue was dissolved in water and DCM and the organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 50-100% to give a gum which was triturated with ether and filtered to give methyl (1aRS,7bSR)-5-[2-(4-ethyl-2-oxopiperazin-1-ylmethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylate (0.312 g) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 9.95 (1H, br, s), 7.81 (1H, dd), 7.26 (2H, m), 6.89 (1H, dd), 6.59 (1H, d), 4.75 (2H, s), 4.29

(1H, d), 3.71 (1H, d), 3.62 (3H, s), 3.15 (4H, m), 2.70 (2H, t), 2.45 (2H, q), 2.02 (1H, m), 1.72 (1H, m), 1.06 (1H, m), 1.02 (3H, t), 0.80 (1H, q).

Intermediate 174

2-(4-Ethyl-2-oxopiperazin-1-ylmethyl)-4-fluorobenzenesulfonyl chloride

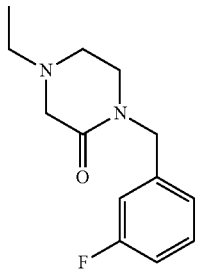


Chlorosulphonic acid (2 mL) was added to 4-ethyl-1-(3-fluorobenzyl)-piperazin-2-one (Intermediate 175, 0.59 g) with stirring and cooling in ice. The cooling was removed and the solution was stirred at room temperature for 4 hours before being carefully added to a mixture of ethyl acetate, ice and sodium bicarbonate. The organic layer was dried (Na_2SO_4) and filtered and the filtrate was concentrated in vacuo to give 2-(4-ethyl-2-oxopiperazin-1-ylmethyl)-4-fluoro-benzenesulfonyl chloride (0.37 g) as a colourless gum.

LCMS (Method E) r/t 1.99 (M–H) 335, 337

Intermediate 175

4-Ethyl-1-(3-fluoro-benzyl)-piperazin-2-one

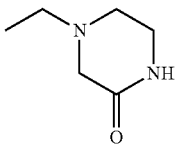


Sodium hydride (60% oil dispersion, 0.176 g) was added to a stirred solution of 4-ethyl-piperazin-2-one (Intermediate 176, 0.512 g) in anhydrous THF (10 mL) and the mixture was stirred at room temperature for 10 minutes. 3-Fluorobenzyl bromide (0.827 g) was added and stirring was continued for 2 hours. The solution was diluted with water and ethyl acetate and the organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-5% to give 4-ethyl-1-(3-fluorobenzyl)piperazin-2-one (0.595 g) as a colourless oil.

^1H NMR ($CDCl_3$) δ: 7.26 (1H, m), 6.91-7.10 (3H, m), 4.61 (2H, s), 3.27 (2H, t), 3.23 (2H, s), 2.65 (2H, t), 2.48 (2H, q), 1.09 (3H, t).

Intermediate 176

4-Ethylpiperazin-2-one

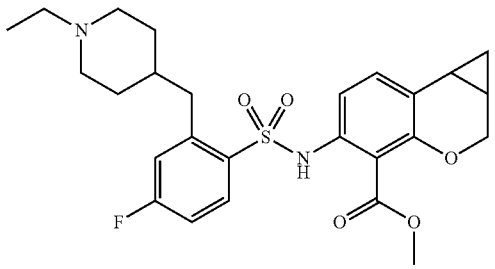


A mixture of 2-oxopiperazine (1.07 g), iodoethane (1.72 g) and potassium carbonate (2.76 g) in acetonitrile (50 mL) was stirred at 55° C. for 3 hours. After cooling, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was triturated with DCM and filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-40% to give 4-ethylpiperazin-2-one (0.991 g) as a colourless oil.

^1H NMR ($CDCl_3$) δ: 6.81 (1H, br, s), 3.37 (2H, m), 3.14 (2H, s), 2.66 (2H, t), 2.50 (2H, q), 1.11 (3H, t).

Intermediate 177

Methyl (1aRS,7bSR)-5-[2-(1-ethylpiperidin-4-ylmethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

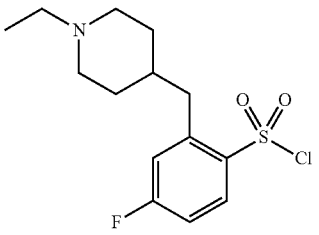


2-(1-Ethylpiperidine-4-ylmethyl)-4-fluorobenzenesulfonyl chloride (Intermediate 178, 0.165 g) was added to a solution of methyl (1aRS,7bSR)-5-amino-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 42, 0.290 g) in DCM (5 mL) and pyridine (1 mL) and the resultant mixture was stirred at room temperature for 21 hours. The mixture was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of 2M NH_3 in methanol and DCM with a gradient of 0-20% to give methyl (1aRS,7bSR)-5-[2-(1-ethyl-piperidin-4-ylmethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (0.200 g) as a solid.

LCMS (Method F) r/t 2.34 (M+H) 503

Intermediate 178

2-(1-Ethylpiperidin-4-ylmethyl)-4-fluorobenzene-sulfonyl chloride

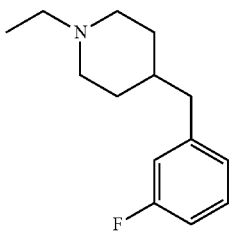


A solution of 1-ethyl-4-(3-fluorobenzyl)piperidine (Intermediate 179, 0.210 g) in DCE (1 mL) was added to chlorosulfonic acid (2 mL) at 0° C. The mixture was allowed to warm to room temperature and stirred for 2 hours. The resultant mixture was added carefully to ice/water and extracted with DCM. The organic layer was dried (Na_2SO_4) and filtered and the filtrate was evaporated to dryness to give 2-(1-ethylpiperidin-4-ylmethyl)-4-fluorobenzenesulfonyl chloride (0.290 g) as a solid.

^{1}H NMR ($CDCl_3$) δ: 8.17 (1H, dd), 7.17 (1H, m), 7.08 (1H, dd), 3.59 (2H, d), 3.13-2.99 (4H, m), 2.57 (2H, m), 2.24 (2H, m), 1.95-1.77 (3H, m), 1.47 (3H, t).

Intermediate 179

1-Ethyl-4-(3-fluorobenzyl)piperidine

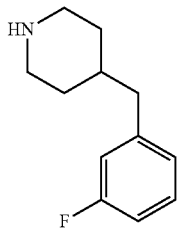


Bromoethane (0.1 mL) was added to a mixture of 4-(3-fluorobenzyl)piperidine (Intermediate 180, 0.259 g) and potassium carbonate (0.204 g) in acetonitrile (10 mL). The mixture was stirred for 20 hours then filtered. The filtrate acidified by addition of few drops of 2M HCl and the solution was passed through a SCX-2 column (10 g). The product was eluted with 2M ammonia in methanol and the residue after evaporation was triturated with diethyl ether. The solid was filtered off and the filtrated was concentrated in vacuo to give 1-ethyl-4-(3-fluorobenzyl)piperidine (0.210 g)

^{1}H NMR ($CDCl_3$) δ: 7.24-7.16 (1H, m), 6.94-6.79 (3H, m), 2.91 (2H, dt), 2.52 (2H, d), 2.36 (2H, q), 1.82 (2H, td), 1.68-1.57 (2H, m), 1.56-1.44 (1H, m), 1.30 (2H, m), 1.06 (3H, t).

Intermediate 180

4-(3-Fluorobenzyl)piperidine

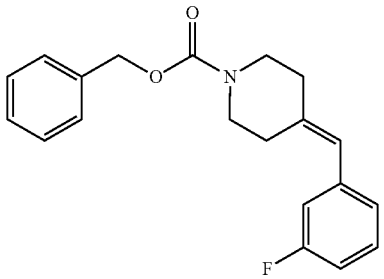


A mixture of benzyl 4-(3-fluorobenzylidene)piperidine-1-carboxylate (Intermediate 181, 1.05 g), 20% palladium hydroxide on carbon (0.227 g), IMS (30 mL) and acetic acid (10 mL) was degassed by nitrogen/vacuum purging. The mixture was placed under an atmosphere of hydrogen with rapid stirring. After 2 hours the mixture was filtered and the filtrate was diluted with water (40 mL) and neutralized with Na_2CO_3. The solution was saturated with sodium chloride, extracted with ethyl acetate dried ($MgSO_4$) and filtered. The filtrate was concentrated in vacuo and the residue was dissolved in a mixture of methanol and water (20 mL, 1:1) and passed down a SCX-2 column. The product was eluted with 2M ammonia to give 4-(3-fluorobenzyl)piperidine (0.532 g)

^{1}H NMR ($CDCl_3$) δ: 7.24-7.16 (1H, m), 6.95-6.77 (3H, m), 3.04 (2H, dt), 2.56 (2H, dd), 2.51 (2H, d), 1.71-1.54 (3H, m), 1.42 (1H, s), 1.14 (2H, m)

Intermediate 181

Benzyl 4-(3-fluorobenzylidene)piperidine-1-carboxylate

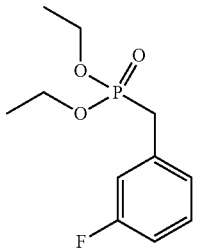


Sodium hydride (0.245 g) was added portionwise to a solution of diethyl (3-fluorobenzyl)phosphonate (Intermediate 182, 1 g) in THF (40 mL) at 0° C. The mixture was stirred for 30 minutes then benzyl 4-oxopiperidine-1-carboxylate (0.947 g) was added at 0° C. The mixture was allowed to warm to room temperature and stirred for 21.5 hours. The mixture was partitioned between water and ethyl acetate and the organic layer was washed with brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-25% to give benzyl 4-(3-fluorobenzylidene)piperidine-1-carboxylate (1.05 g)

^{1}H NMR ($CDCl_3$) δ: 7.39-7.22 (6H, m), 6.98-6.83 (3H, m), 6.33 (1H, s), 5.15 (2H, s), 3.54 (4H, dt), 2.41 (4H, dt).

Intermediate 182

Diethyl (3-fluorobenzyl)phosphonate

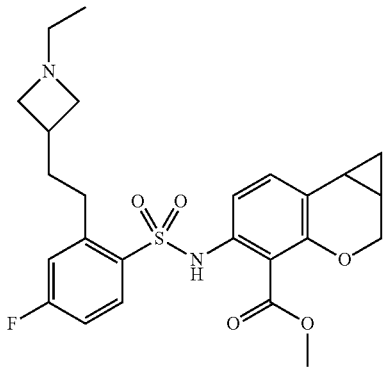


A mixture of 3-fluorobenzyl bromide (2 g) and triethyl phosphite (2.2 mL) was heated at 160° C. under nitrogen for 4 hours. After cooling, the were volatiles removed in vacuo and the residue was purified by chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-100% to give diethyl (3-fluorobenzyl)phosphonate (2.46 g)

^{1}H NMR ($CDCl_3$) δ: 7.31-7.22 (1H, m), 7.11-6.89 (3H, m), 4.09-3.97 (4H, m), 3.13 (2H, d), 1.25 (6H, t).

Intermediate 183

Methyl (1aRS,7bSR)-5-{2-[2-(1-ethylazetidin-3-yl) ethyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

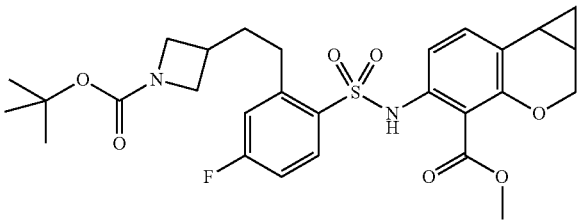


A solution of tert-butyl (1aRS,7bSR)-3-{2-[5-fluoro-2-(4-methoxycarbonyl-1,1a,2,7b-tetrahydrocyclopropa[c] chromen-5-ylsulfamoyl)phenyl]ethyl}azetidine-1-carboxylate (Intermediate 184, 0.397 g) in DCM (5 mL) and trifluoroacetic acid (5 mL) was left at room temperature for 30 minutes then evaporated in vacuo and the residue was dissolved in toluene and re-evaporated. The residue was dissolved in DCM (15 mL) and acetaldehyde (0.063 g) was added followed by sodium triacetoxyborohydride (0.301 g). The mixture was stirred at room temperature for 2 hours then diluted with ethyl acetate and water and the organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-25% to give methyl (1aRS,7bSR)-5-{2-[2-(1-ethylazetidin-3-yl)ethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.312 g) as a white foam.

LCMS (Method E) r/t 2.75 (M+H) 489.

Intermediate 184

tert-butyl (1aRS,7bSR)-3-{2-[5-fluoro-2-(4-methoxycarbonyl-1,1a,2,7b-tetrahydro-cyclopropa[c] chromen-5-ylsulfamoyl)phenyl]ethyl}azetidine-1-carboxylate

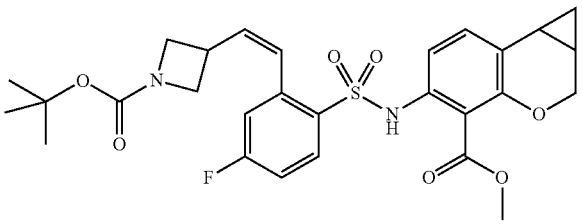


A mixture of tert-butyl (1aRS,7bSR)-3-{(E/Z)-2-[5-fluoro-2-(4-methoxycarbonyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromen-5-ylsulfamoyl)phenyl]vinyl}azetidine-1-carboxylate (Intermediate 185, 0.502 g) and 10% palladium on carbon (0.05 g) in ethanol (25 mL) was stirred under an atmosphere of hydrogen for 30 minutes. The suspension was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-40% to give tert-butyl (1aRS,7bSR)-3-{2-[5-fluoro-2-(4-methoxycarbonyl-1,1a,2,7b-tetrahydrocyclopropa[c] chromen-5-ylsulfamoyl)phenyl]-ethyl}azetidine-1-carboxylate (0.401 g) as a colourless gum.

^{1}H NMR ($CDCl_3$) δ: 9.01 (1H, br, s), 7.90 (1H, dd), 7.21 (1H, d), 7.02 (1H, d), 6.94 (2H, m), 4.32 (1H, d), 4.00 (2H, t), 3.79 (1H, d), 3.77 (3H, s), 3.56 (2H, dd), 2.79 (2H, dd), 2.56 (1H, m), 1.89 (3H, m), 1.72 (1H, m), 1.45 (9H, s), 0.99 (2H, m).

Intermediate 185

tert-Butyl (1aRS,7bSR)-3-{(E/Z)-2-[5-fluoro-2-(4-methoxycarbonyl-1,1a,2,7b-tetrahydro-cyclopropa[c] chromen-5-ylsulfamoyl)phenyl]vinyl}azetidine-1-carboxylate



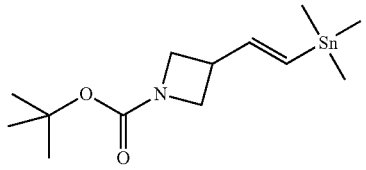
A mixture of methyl (1aRS,7bSR)-5-(2-bromo-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa [c]chromene-4-carboxylate (Intermediate 41, 0.456 g), tert-butyl 3-((E/Z)-2-trimethylstannanylvinyl)azetidine-1-carboxylate (Intermediate 186, 0.433 g), tris (dibenzylideneacetone)dipalladium(0) (0.046 g) and tri-tert-butylphosphonium tetrafluoroborate (0.029 g) in dioxane (15 mL) and DMSO (1.5 mL) was stirred and heated at 90° C.

under nitrogen for 1 hour. After cooling, the solution was diluted with ethyl acetate, washed with water, dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-40% to give tert-butyl (1aRS,7bSR)-3-{(E/Z)-2-[5-fluoro-2-(4-methoxycarbonyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromen-5-ylsulfamoyl)phenyl]vinyl}-azetidine-1-carboxylate (0.508 g) as a colourless gum.

LCMS (Method E) r/t 4.47 (M–H) 557

Intermediate 186

tert-Butyl 3-((E/Z)-2-trimethylstannanylvinyl)azetidine-1-carboxylate

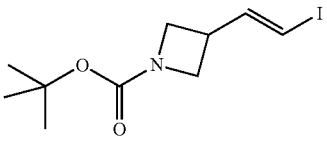


A solution of tert-butyl 3-((E/Z)-2-iodovinyl)azetidine-1-carboxylate (Intermediate 187, 1.39 g), hexamethylditin (2.95 g), and tetrakis(triphenylphosphine)palladium(0) (0.52 g) in anhydrous THF (40 mL) was stirred and heated at 50° C. under nitrogen for 2 hours. After cooling, the mixture was evaporated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-10% to give tert-butyl 3-((E/Z)-2-trimethylstannanylvinyl)azetidine-1-carboxylate (0.601 g) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 5.79-6.5 (2H, m), 3.95 (2H, m), 3.62 (2H, m), 2.88-3.12 (1H, m), 1.32 (9H, s), 0.0 (9H, s).

Intermediate 187

tert-Butyl 3-((E/Z)-2-iodovinyl)azetidine-1-carboxylate

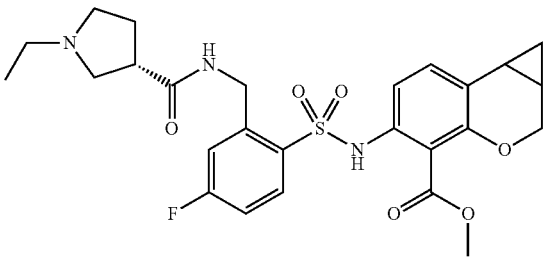


A solution of tert-butyl 3-formylazetidine-1-carboxylate (1.97 g) and iodoform (8.37 g) in anhydrous THF (25 mL) was added to a stirred suspension of anhydrous chromium(II) chloride in anhydrous THF (100 mL) under nitrogen and the mixture was stirred at room temperature for 4 hours. The resulting mixture was diluted with water and ethyl acetate and the organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-15% to give tert-butyl 3-((E/Z)-2-iodovinyl)azetidine-1-carboxylate (2.01 g) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 6.71 (0.8H, dd), 6.55 (0.2H, t), 6.33 (0.2H, d), 6.18 (0.8H, d), 4.20 (0.4H, t), 4.08 (1.6H, t), 3.76 (2H, m), 3.45 (0.2H, m), 3.19 (0.8H, m), 1.44 (9H, s).

Intermediate 188

Methyl (1aRS,7bSR)-5-(2-{[((S)-1-ethylpyrrolidine-3-carbonyl)amino]-methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

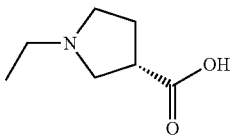


HATU (0.234 g) was added to a mixture of (S)-1-ethylpyrrolidine-3-carboxylic acid (Intermediate 189, 0.089 g) and NMM (0.068 mL) in DMF (4 mL) and the mixture was stirred for 15 minutes. Methyl (1aRS,7bSR)-5-(2-aminomethyl-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 102, 0.250 g) was added and the mixture was stirred for 20 hours. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of 2M ammonia in methanol and DCM with a gradient of 0-15% to give methyl (1aRS,7bSR)-5-(2-{[(S)-1-ethylpyrrolidine-3-carbonyl)amino]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.190 g) as a solid.

^{1}H NMR ($CDCl_3$) δ: 7.81 (1H, dd), 7.46-7.38 (1H, m), 7.30-7.20 (3H, m), 7.06-6.93 (2H, m), 4.58 (2H, d), 4.32 (1H, dd), 3.79 (1H, dd), 3.76 (3H, s), 2.93-2.78 (3H, m), 2.70-2.49 (4H, m), 2.24-2.08 (1H, m), 2.00-1.87 (2H, m), 1.78-1.68 (1H, m), 1.15 (3H, t), 1.06-0.98 (2H, m)

Intermediate 189

(S)-1-Ethyl-pyrrolidine-3-carboxylic acid

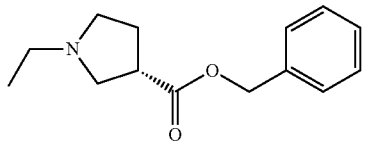


A mixture of benzyl (S)-1-ethylpyrrolidine-3-carboxylate (Intermediate 190, 0.563 g), 20% palladium hydroxide on carbon (0.056 g), ethyl acetate (9 mL) and IMS (1 mL) was degassed and hydrogenated for 4 hours. The catalyst was removed by filtration, washed with ethyl acetate and the filtrate was concentrated in vacuo to give (S)-1-ethylpyrrolidine-3-carboxylic acid (0.318 g) as a solid.

^{1}H NMR ($CDCl_3$) δ: 12.46-10.55 (1H, br s), 3.84-3.57 (1H, br s), 3.49-3.26 (1H, br s), 3.26-2.93 (5H, m), 2.50-2.33 (1H, m), 2.28-2.11 (1H, m), 1.35 (3H, t).

Intermediate 190

Benzyl (S)-1-ethylpyrrolidine-3-carboxylate

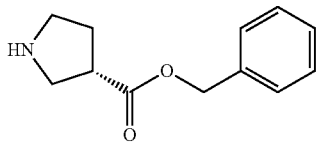


Ethyl bromide (0.21 mL) was added to a mixture of benzyl (S)-pyrrolidine-3-carboxylate trifluoroacetic acid salt (Intermediate 191, 0.897 g), potassium carbonate (0.971 g) and DMF (10 mL) at room temperature and the mixture was stirred for 25 hours. Further ethyl bromide (0.11 mL) was added and stirring was continued for 24 hours. Further ethyl bromide (0.05 mL) was added and stirring was continued for 22 hours. The resultant mixture was diluted with water and extracted with diethyl ether, washed with brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo to give benzyl (S)-1-ethylpyrrolidine-3-carboxylate (0.563 g).

^{1}H NMR ($CDCl_3$) δ: 7.38-7.30 (5H, m), 5.13 (2H, s), 3.09 (1H, m), 2.93 (1H, t), 2.76-2.66 (1H, m), 2.63 (1H, dd), 2.56-2.41 (3H, m), 2.16-2.05 (2H, m), 1.10 (3H, t).

Intermediate 191

Benzyl (S)-pyrrolidine-3-carboxylate trifluoroacetic acid salt

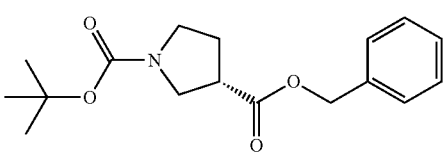


Trifluoroacetic acid (2.5 mL) was added to a solution of benzyl (S)-1-tert-butoxycarbonylpyrrolidine-3-carboxylate (Intermediate 192, 0.859 g) and DCM (10 mL) at room tempertaure. The mixture was stirred for 4 hours then concentrated in vacuo. The residue was azetroped with toluene then ethyl acetate to give benzyl (S)-pyrrolidine-3-carboxylate trifluoroacetic acid salt (1 g).

^{1}H NMR ($CDCl_3$) δ: 7.41-7.29 (5H, m), 5.16 (2H, dd), 3.64-3.45 (2H, m), 3.44-3.23 (3H, m), 2.42-2.20 (2H, m).

Intermediate 192

Benzyl
(S)-1-tert-butoxycarbonylpyrrolidine-3-carboxylate

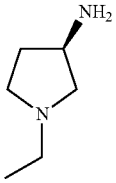


DBU (0.764 mL) was added to a mixture of benzyl bromide (0.61 mL), (S)-1-tert-butoxycarbonyl-pyrrolidine-3-carboxylic acid (1 g) in anhydrous toluene (10 mL) and the mixture was stirred at room temperature for 24 hours. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-35% to give benzyl (S)-1-tert-butoxycarbonylpyrrolidine-3-carboxylate (0.859 g)

^{1}H NMR ($CDCl_3$) δ: 7.39-7.29 (5H, m), 5.14 (2H, s), 3.70-3.41 (3H, m), 3.41-3.27 (1H, m), 3.08 (1H, m), 2.13 (2H, q), 1.45 (9H, s).

Intermediate 193

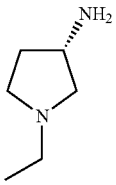
(R)-1-Ethylpyrrolidin-3-ylamine



Acetyl chloride (15 mL) was added to methanol (120 mL) and the resultant solution was stirred for 20 minutes. A solution of tert-butyl N—((R)-1-ethylpyrrolidin-3-yl)carbamate (Intermediate 94, 8.4 g) in methanol (30 mL) was then added and the mixture was stirred and heated at 80° C. overnight. After cooling, the mixture was concentrated under vacuum and the residue was redissolved in methanol (150 mL) and potassium carbonate (25.8 g) was added. The mixture was stirred and heated at 30° C. for 30 hours. After cooling, the solid was filtered off and the filtrate was distilled, collecting the product at 100° C. to give (R)-1-ethylpyrrolidin-3-ylamine (2.10 g) as a yellow oil, which was used without further characterisation.

Intermediate 194

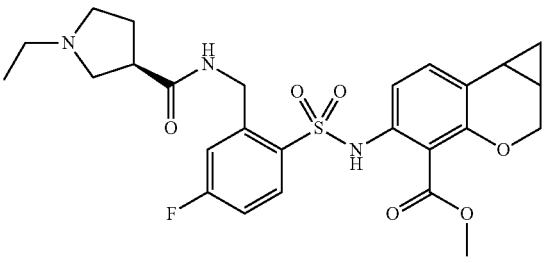
(S)-1-Ethylpyrrolidin-3-ylamine



Prepared by proceeding in a similar manner to Intermediate 193, starting from tert-butyl N—((S)-1-ethylpyrrolidin-3-yl)carbamate (Intermediate 82) and used without further characterisation.

Intermediate 195

Methyl (1aRS,7bSR)-5-(2-{[(R)-1-ethylpyrrolidine-3-carbonyl)amino]-methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

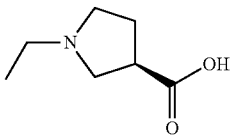


Prepared by proceeding in a similar manner to Intermediate 188, starting from methyl (1aRS,7bSR)-5-(2-aminomethyl-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (intermediate 102) and (R)-1-ethylpyrrolidine-3-carboxylic acid (Intermediate 196).

^{1}H NMR ($CDCl_3$) δ: 7.81 (1H, dd), 7.43-7.34 (1H, m), 7.30-7.20 (3H, m), 7.05-6.93 (2H, m), 4.59 (2H, d), 4.32 (1H, dd), 3.79 (1H, dd), 3.76 (3H, s), 2.99-2.84 (3H, m), 2.81-2.73 (1H, m), 2.73-2.60 (3H, m), 2.27-2.12 (1H, m), 2.01-1.88 (2H, m), 1.78-1.67 (1H, m), 1.17 (3H, s), 1.08-0.98 (2H, m).

Intermediate 196

(R)-1-Ethylpyrrolidine-3-carboxylic acid

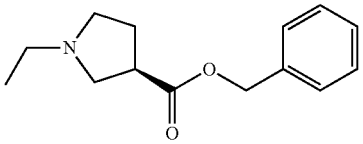


Prepared by proceeding in a similar manner to Intermediate 189, starting from benzyl (R)-1-ethylpyrrolidine-3-carboxylate (Intermediate 197).

^{1}H NMR ($CDCl_3$) δ: 11.05-9.55 (1H, br s), 3.71 (1H, br s), 3.37 (1H, br s), 3.27-2.94 (5H, m), 2.49-2.32 (1H, m), 2.29-2.13 (1H, m), 1.35 (3H, t).

Intermediate 197

Benzyl (R)-1-ethylpyrrolidine-3-carboxylate

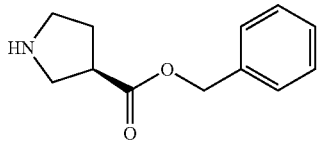


Prepared by proceeding in a simialr manner to Intermediate 190, starting from benzyl (R)-pyrrolidine-3-carboxylate trifluoroacetic acid salt (Intermediate 198).

^{1}H NMR ($CDCl_3$) δ: 7.38-7.30 (5H, m), 5.13 (2H, s), 3.09 (1H, m), 2.93 (1H, t), 2.76-2.66 (1H, m), 2.63 (1H, dd), 2.52-2.42 (3H, m), 2.16-2.06 (2H, m), 1.11 (3H, t).

Intermediate 198

Benzyl (R)-pyrrolidine-3-carboxylic trifluoroacetic acid salt

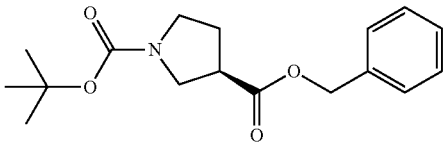


Prepared by proceeding in a similar manner to Intermediate 191, starting from benzyl (R)-1-tert-butoxycarbonylpyrrolidine-3-carboxylate (Intermediate 199).

^{1}H NMR ($CDCl_3$) δ: 7.41-7.29 (5H, m), 5.16 (2H, dd), 3.64-3.45 (2H, m), 3.42-3.23 (3H, m), 2.41-2.20 (2H, m).

Intermediate 199

Benzyl (R)-1-tert-butoxycarbonylpyrrolidine-3-carboxylate

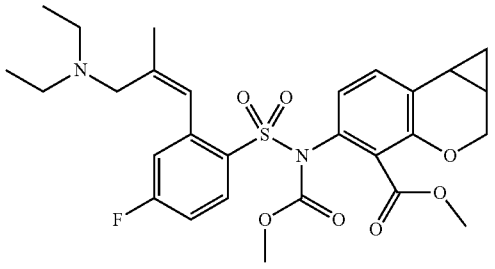


Prepared by proceeding in a similar manner to Intermediate 192, starting from (R)-1-tert-butoxycarbonyl-pyrrolidine-3-carboxylic acid.

^{1}H NMR ($CDCl_3$) δ: 7.42-7.29 (5H, m), 5.15 (2H, s), 3.72-3.42 (3H, m), 3.42-3.26 (1H, m), 3.08 (1H, m), 2.13 (2H, q), 1.45 (9H, s).

Intermediate 200

Methyl (1aRS,7bSR)-5-{N-[2-((Z)-3-diethylamino-2-methylprop-1-enyl)-4-fluorobenzenesulfonyl]-N-(methoxycarbonyl)amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate



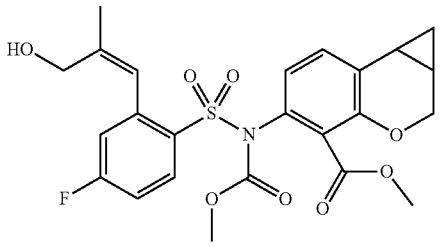
Methanesulphonic anhydride (0.159 g) was added to a solution of methyl (1aRS,7bSR)-5-{N-[4-fluoro-2-((Z)-3-hydroxy-2-methylprop-1-enyl)benzenesulfonyl]-N-(methoxycarbonyl)amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 201, 0.310 g) and N,N-diisopropyl-N-ethylamine (0.118 g) in DCM (10 mL) and the mixture was left at room temperature for 1 hour. Diethylamine (1 mL) was added and the solution was left for

a further 16 hours. The mixture was washed with water and filtered through a phase separator. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-8% to give methyl (1aRS,7bSR)-5-{N-[2-((Z)-3-diethylamino-2-methylprop-1-enyl)-4-fluorobenzene-sulfonyl]-N-methoxy-carbonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.268 g) as a white foam.

LCMS (Method E) r/t 2.79 (M+H) 561.

Intermediate 201

Methyl (1aRS,7bSR)-5-{N-[4-fluoro-2-((Z)-3-hydroxy-2-methylprop-1-enyl)benzenesulfonyl]-N-(methoxycarbonyl)amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

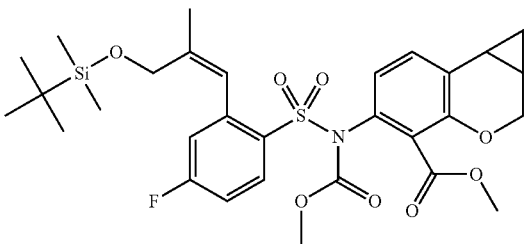


Concentrated hydrochloric acid (1 mL) was added to a solution of methyl (1aRS,7bSR)-5-(N-{2[(Z)-3-(tert-butyldimethylsilanyloxy)-2-methylprop-1-enyl]-4-fluorobenzenesulfonyl]-N-methoxycarbonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 202, 0.385 g) in methanol (20 mL) and the mixture was left at room temperature for 45 minutes. The solution was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-60% to give methyl (1aRS,7bSR)-5-{N-[4-fluoro-2-((Z)-3-hydroxy-2-methylprop-1-enyl)benzenesulfonyl]-N-methoxycarbonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (0.314 g) as a white foam.

^{1}H NMR ($CDCl_3$) δ: 8.18 (1H, dd), 7.35 (1H, d), 7.11 (1H, dt), 6.94 (1H, d), 6.89 (1H, d), 6.74 (1H, s), 4.39 (1H, d), 3.82-4.17 (3H, m), 3.76 (1.5H, s), 3.72 (1.5H, s), 3.64 (3H, s), 1.98 (4H, m), 1.82 (1H, q), 1.14 (2H, m).

Intermediate 202

Methyl (1aRS,7bSR)-5-(N-{2[(Z)-3-(tert-butyldimethylsilanyloxy)-2-methylprop-1-enyl]-4-fluorobenzenesulfonyl]-N-(methoxycarbonyl)amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate

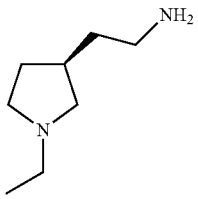


A mixture of methyl (1aRS,7bSR)-5-[N-(2-bromo-4-fluorobenzenesulfonyl)-N-(methoxy-carbonyl)amino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylate (Intermediate 65, 0.257 g), tert-butyl-dimethyl-((Z)-2-methyl-3-tributylstannanylallyloxy)silane (0.475 g), tris(dibenzylideneacetone)dipalladium(0) (0.023 g) and tri-tert-butylphosphonium tetrafluoroborate (0.015 g) in dioxane (8 mL) and DMSO (0.8 mL) was stirred and heated at 90° C. under nitrogen for 1 hour. Further tris(dibenzylideneacetone) dipalladium(0) (0.023 g) and tri-tert-butylphosphonium tetrafluoroborate (0.015 g) were added and heating was continued for a further 40 minutes. After cooling, the mixture was diluted with ethyl acetate, washed with water, dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-20% to give methyl (1aRS,7bSR)-5-(N-{2[(Z)-3-(tert-butyldimethylsilanyloxy)-2-methylprop-1-enyl]-4-fluorobenzenesulfonyl]-N-methoxycarbonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.231 g) as a colourless gum.

LCMS (Method E) r/t 5.22 (M+Na) 642.

Intermediate 203

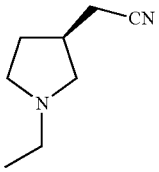
2-((R)-1-Ethylpyrrolidin-3-yl)ethylamine



Lithium aluminium hydride (1.0 g) was added in portions to a stirred, cooled solution of 2-((S)-1-ethylpyrrolidin-3-yl) acetonitrile (Intermediate 204, 3.8 g) in THF (20 mL) at 0° C. On completion of the addition, the mixture was stirred at room temperature for 4 hours. Water was added cautiously, followed by addition of 15% aqueous sodium hydroxide solution and more water. The solid was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in DCM, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give 2-((R)-1-ethylpyrrolidin-3-yl)ethylamine (2.0 g) as a colourless oil, which was used without further characterisation.

Intermediate 204

2-((S)-1-Ethylpyrrolidin-3-yl)acetonitrile

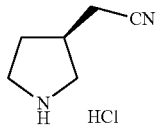


Iodoethane (10.1 g) was added to a mixture of 2-((S)-pyrrolidin-3-yl)acetonitrile hydrochloride (Intermediate 205,

7.9 g) and potassium carbonate (29.7 g) in DMF (20 mL) and the resultant mixture was stirred at room temperature for 5 hours. Water was added and the mixture was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give 2-((S)-1-ethylpyrrolidin-3-yl)acetonitrile (3.8 g) as a yellow oil which was used without further characterisation.

Intermediate 205

2-((S)-Pyrrolidin-3-yl)acetonitrile hydrochloride

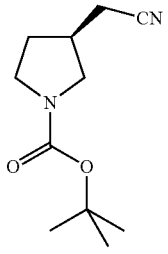


A solution of tert-butyl (S)-3-cyanomethylpyrrolidine-1-carboxylate

(Intermediate 206, 12.3 g) in methanol (150 mL) and concentrated hydrochloric acid (12 mL) was stirred and heated at 50° C. overnight. After cooling, the mixture was concentrated under vacuum to give crude 2-((S)-pyrrolidin-3-yl)acetonitrile hydrochloride (9.0 g) as a white solid which was used without further characterisation.

Intermediate 206

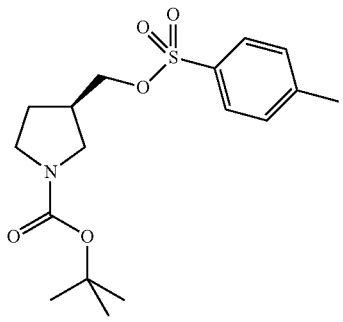
tert-Butyl
(S)-3-cyanomethylpyrrolidine-1-carboxylate



A mixture of tert-butyl ((R)-3-(4-methylbenzenesulfonyloxymethyl)pyrrolidine-1-carboxylate (Intermediate 207, 22.3 g) and sodium cyanide (6.13 g) in DMSO (100 mL) was stirred and heated at 100° C. for 4 hours. After cooling, a saturated aqueous solution of iron (II) sulphate was added and the mixture was stirred at room temperature for 8 hours. The resultant mixture was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with an mixture of ethyl acetate and petroleum ether (20%) to give tert-butyl (S)-3-cyanomethylpyrrolidine-1-carboxylate (12.3 g) as a white solid which was used without further characterisation.

Intermediate 207

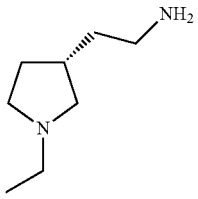
tert-Butyl ((R)-3-(4-methylbenzenesulfonyloxymethyl)-pyrrolidine-1-carboxylate



Prepared by proceeding in a similar manner to Intermediate 140, starting from tert-butyl (R)-3-hydroxymethylpyrrolidine-1-carboxylate and 4-methylbenzenesulfonyl chloride and used without further characterisation.

Intermediate 208

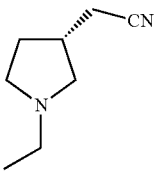
2-((S)-1-Ethylpyrrolidin-3-yl)ethylamine



Prepared by proceeding in a similar manner to Intermediate 203, starting from 2-((R)-1-ethylpyrrolidin-3-yl)acetonitrile (Intermediate 209) and used without further characterisation.

Intermediate 209

2-((R)-1-Ethylpyrrolidin-3-yl)acetonitrile

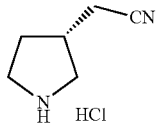


Iodoethane (6.46 g) was added in portions to a cooled mixture of 2-((R)-pyrrolidin-3-yl)acetonitrile (Intermediate 210, 4.6 g) and potassium carbonate (8.6 g) in acetonitrile (30 mL) at 0° C. The mixture was stirred for 3 hours at 0° C. then concentrated under vacuum. The residue was partitioned

between water and DCM. The organic layer was washed with brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give 2-((R)-1-ethylpyrrolidin-3-yl)acetonitrile (2.1 g) as a colourless liquid which was used without further characterisation.

Intermediate 210

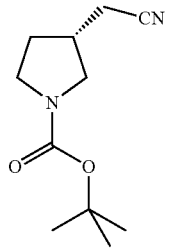
2-((R)-Pyrrolidin-3-yl)acetonitrile hydrochloride



Prepared by proceeding in a similar manner to Intermediate 205, starting from tert-butyl (R)-3-cyanomethylpyrrolidine-1-carboxylate (Intermediate 211) and used without further characterisation.

Intermediate 211

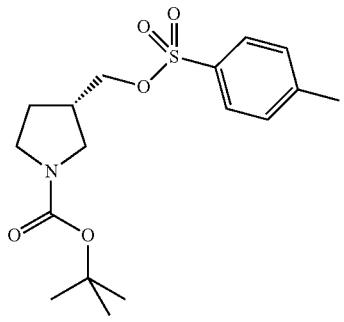
tert-Butyl
(R)-3-cyanomethylpyrrolidine-1-carboxylate



Prepared by proceeding in a similar manner to Intermediate 206, starting from tert-butyl ((S)-3-(4-methylbenzenesulfonyloxymethyl)pyrrolidine-1-carboxylate (Intermediate 212) and used without further characterisation.

Intermediate 212

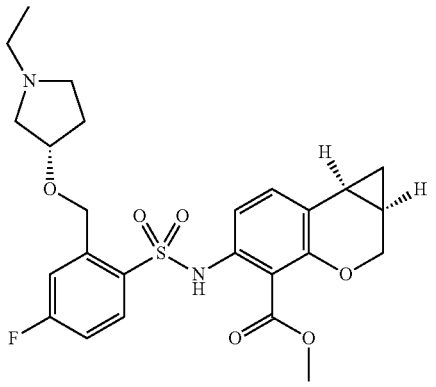
tert-Butyl ((S)-3-(4-methylbenzenesulfonyloxymethyl)-pyrrolidine-1-carboxylate



Prepared by proceeding in a similar manner to Intermediate 140, starting from tert-butyl (S)-3-hydroxymethylpyrrolidine-1-carboxylate and 4-methylbenzenesulfonyl chloride and used without further characterisation.

Intermediate 213

Methyl (1aR,7bS)-5-[2-((S)-1-ethylpyrrolidin-3-yloxymethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

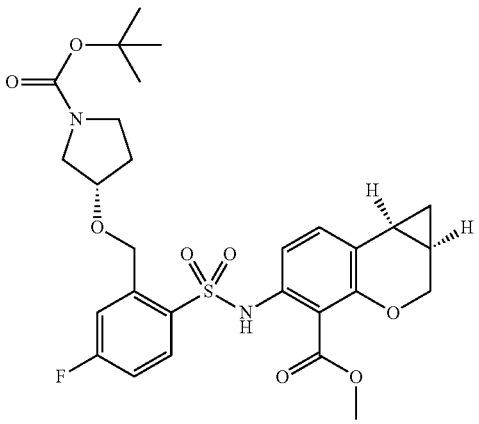


A solution of tert-butyl (S)-3-[(1aR,7bS)-5-fluoro-2-(4-methoxycarbonyl-1,1a,2,7b-tetrahydro-cyclopropa[c]chromen-5-ylsulfamoyl)benzyloxy]pyrrolidine-1-carboxylate (Intermediate 214, 0.284 g) in trifluoroacetic acid (4 mL) and DCM (4 mL) was left at room temperature for 30 minutes. The mixture was evaporated in vacuo and the residue was azeotroped with toluene. The residue was dissolved in DCM (4 mL) and acetaldehyde (0.044 g) was added followed by sodium triacetoxyborohydride (0.212 g). The mixture was stirred at room temperature for 1 hour. The resulting solution was diluted with DCM and 1M sodium hydroxide solution and the organic layer was dried (Na_2SO_4) and filtered. The filtrate was evaporated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of methanol and DCM with a gradient of 0-20% to give methyl (1aR,7bS)-5-[2-((S)-1-ethylpyrrolidin-3-yloxymethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.221 g) as a white foam.

^1H NMR ($CDCl_3$) δ: 7.76 (1H, dd), 7.32 (1H, dd), 7.16 (1H, d), 6.94 (1H, dt), 6.87 (1H, d), 4.86 (1H, d), 4.68 (1H, d), 4.32 (1H, d), 4.19 (1H, m), 3.79 (1H, d), 3.73 (3H, s), 3.13 (1H, d), 2.92 (1H, q), 2.35-2.75 (4H, m), 2.10 (2H, m), 1.92 (1H, m), 1.72 (1H, m), 1.14 (3H, t), 1.03 (2H, m).

Intermediate 214

tert-Butyl (S)-3-[(1aR,7bS)-5-fluoro-2-(4-methoxycarbonyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromen-5-ylsulfamoyl)benzyloxy]pyrrolidine-1-carboxylate

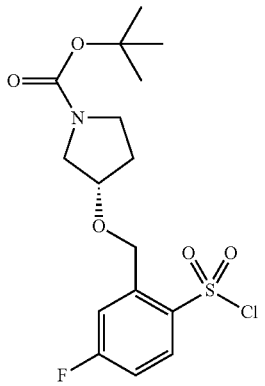


A solution of tert-butyl (S)-3-(2-chlorosulfonyl-5-fluorobenzyloxy)pyrrolidine-1-carboxylate (Intermediate 215, 0.295 g) in DCM (2 mL) was added to a solution of methyl (1aR,7bS)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 42A, 0.11 g) in DCM (2 mL) and the mixture was left at room temperature for 5 days. The mixture was diluted with DCM, washed with 1M hydrochloric acid and filtered through a phase separator. The filtrate was evaporated in vacuo and the residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-30% to give tert-butyl (S)-3-[5-fluoro-2-((1aR,7bS)-4-methoxycarbonyl-1,1a,2,7b-tetrahydrocyclopropa-[c]chromen-5-ylsulfamoyl) benzyloxy]pyrrolidine-1-carboxylate (0.288 g) as a white foam.

^{1}H NMR ($CDCl_3$) δ: 8.86 (1H, br, s), 7.76 (1H, dd), 7.41 (1H, dd), 7.25 (1H, d), 7.07 (1H, d), 6.95 (1H, dt), 4.69-4.91 (2H, br, q), 4.32 (1H, d), 4.19 (1H, m), 3.77 (1H, d), 3.71 (3H, s), 3.49 (4H, br, m), 1.89-2.18 (3H, m), 1.73 (1H, m), 1.47 (9H, s), 1.00 (2H, m).

Intermediate 215

tert-Butyl (S)-3-(2-chlorosulfonyl-5-fluorobenzyloxy)pyrrolidine-1-carboxylate

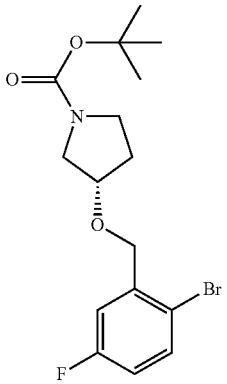


n-Butyllithium (1.6M in hexanes, 3.3 mL) was added to a solution of tert-butyl (S)-3-(2-bromo-5-fluorobenzyloxy) pyrrolidine-1-carboxylate (Intermediate 216, 1.87 g), in anhydrous THF (20 mL) at −78° C. under an atmosphere of nitrogen and the mixture was stirred for 30 minutes. Sulphur dioxide was passed through the resulting solution for 30 minutes, then the cooling bath was removed and the mixture was allowed to warm to room temperature and stirred for 15 minutes. The solution was evaporated in vacuo and the residue was dissolve in DCM (20 mL) and N-chlorosuccinimide (0.668 g) was added. The mixture was stirred for 30 minutes then diluted with ether and water. The organic layer was dried ($MgSO_4$) and filtered and the filtrate was evaporated in vacuo. The residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-25% to give tert-butyl (S)-3-(2-chlorosulfonyl-5-fluorobenzyloxy)pyrrolidine-1-carboxylate (1.01 g) as a colourless, viscous oil.

^{1}H NMR ($CDCl_3$) δ: 8.09 (1H, dd), 7.58 (1H, dd), 7.18 (1H, dt), 4.98 (2H, q), 4.28 (1H, m), 3.40-3.61 (4H, m), 1.92-2.20 (2H, m), 1.47 (9H, s).

Intermediate 216

tert-Butyl (S)-3-(2-bromo-5-fluorobenzyloxy)pyrrolidine-1-carboxylate

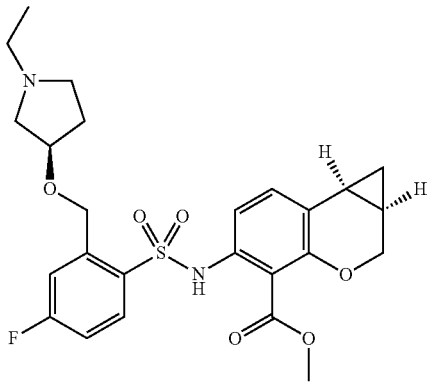


Sodium hydride (60% oil dispersion, 0.24 g) was added to a stirred solution of tert-butyl (S)-3-hydroxypyrrolidine-1-carboxylate (0.935 g) in THF (15 mL) and the mixture was stirred for 5 minutes. 2-Bromo-5-fluorobenzyl bromide (1.608 g) was added and stirring was continued for 20 hours. The resultant suspension was filtered and the filtrate was evaporated to dryness. The residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 0-15% to give tert-butyl (S)-3-(2-bromo-5-fluorobenzyloxy)-pyrrolidine-1-carboxylate (1.88 g) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ: 7.46 (1H, dd), 7.22 (1H, dd), 6.88 (1H, dt), 4.52 (2H, s), 4.19 (1H, m), 3.40-3.65 (4H, br, m), 1.91-2.18 (2H, m), 1.49 (9H, s).

Intermediate 217

Methyl (1aR,7bS)-5-[2-((R)-1-ethylpyrrolidin-3-yloxymethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

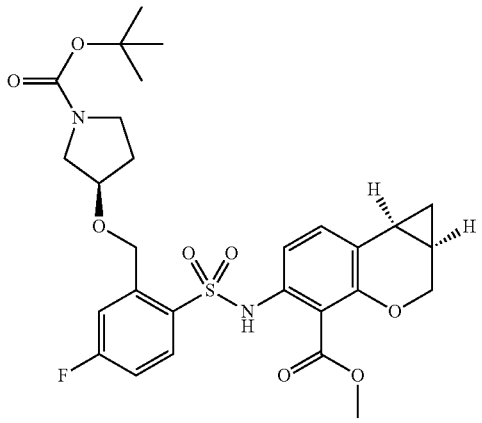


Prepared by proceeding in a similar manner to Intermediate 213, starting from tert-butyl (R)-3-[(1aR,7bS)-5-fluoro-2-(4-methoxycarbonyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromen-5-ylsulfamoyl)benzyloxy]-pyrrolidine-1-carboxylate (Intermediate 218).

^{1}H NMR ($CDCl_3$) δ: 7.76 (1H, dd), 7.32 (1H, dd), 7.17 (1H, d), 6.95 (1H, dt), 6.88 (1H, d), 4.85 (1H, d), 4.68 (1H, d), 4.32 (1H, d), 4.18 (1H, m), 3.81 (1H, d), 3.72 (3H, s), 3.11 (1H, d), 2.92 (1H, q), 2.25-2.75 (4H, m), 2.09 (2H, m), 1.91 (1H, m), 1.72 (1H, m), 1.14 (3H, t), 1.03 (2H, m).

Intermediate 218

tert-Butyl (R)-3-[(1aR,7bS)-5-fluoro-2-(4-methoxycarbonyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromen-5-ylsulfamoyl)benzyloxy]pyrrolidine-1-carboxylate

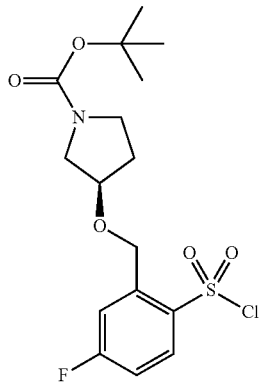


Prepared by proceeding in a similar manner to Intermediate 214, starting from tert-butyl (R)-3-(2-chlorosulfonyl-5-fluorobenzyloxy)pyrrolidine-1-carboxylate (Intermediate 219) and methyl (1aR,7bS)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 42A).

^{1}H NMR ($CDCl_3$) δ: 8.86 (1H, br, s), 7.76 (1H, dd), 7.41 (1H, dd), 7.25 (1H, d), 7.07 (1H, d), 6.95 (1H, dt), 4.78 (2H, br, s), 4.32 (1H, d), 4.19 (1H, m), 3.77 (1H, d), 3.71 (3H, s), 3.49 (4H, br, m), 1.89-2.18 (3H, m), 1.73 (1H, m), 1.47 (9H, s), 1.00 (2H, m).

Intermediate 219

tert-Butyl (R)-3-(2-chlorosulfonyl-5-fluorobenzyloxy)pyrrolidine-1-carboxylate

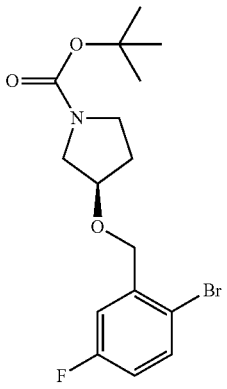


Prepared by proceeding in a similar manner to Intermediate 215, starting from tert-butyl (R)-3-(2-bromo-5-fluorobenzyloxy)pyrrolidine-1-carboxylate (Intermediate 220).

^{1}H NMR ($CDCl_3$) δ: 8.10 (1H, dd), 7.58 (1H, dd), 7.17 (1H, dt), 4.99 (2H, q), 4.28 (1H, m), 3.40-3.61 (4H, m), 1.92-2.20 (2H, m), 1.48 (9H, s).

Intermediate 220

tert-Butyl (R)-3-(2-bromo-5-fluorobenzyloxy)pyrrolidine-1-carboxylate

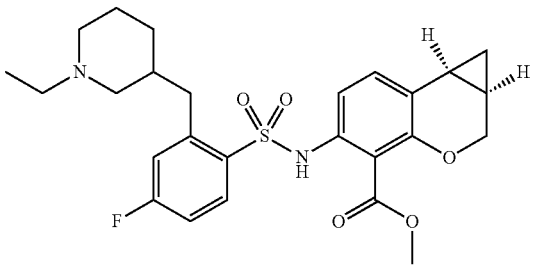


Prepared by proceeding in a similar manner to Intermediate 216, starting from tert-butyl(R)-3-hydroxy-pyrrolidine-1-carboxylate.

^{1}H NMR ($CDCl_3$) δ: 7.46 (1H, dd), 7.22 (1H, dd), 6.88 (1H, dt), 4.52 (2H, s), 4.19 (1H, m), 3.40-3.65 (4H, br, m), 1.91-2.18 (2H, m), 1.49 (9H, s).

Intermediate 221

Methyl (1aR,7bS)-5-[2-(1-ethylpiperidin-3-ylmethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

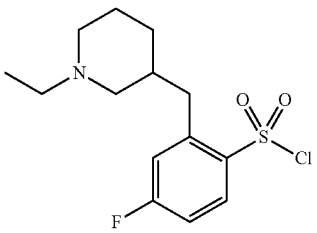


2-(1-Ethylpiperidin-3-ylmethyl)-4-fluorobenzenesulfonyl chloride (Intermediate 222, 0.21 g) was added to a solution of methyl (1aR,7bS)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 42A 0.290 g) in DCM (10 mL) and pyridine (2 mL) and the resultant mixture was stirred at room temperature for 4 hours. The mixture was evaporated to dryness and the residue was partitioned between DCM and water. The organic layer was dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica eluting with a mixture of 2M ammonia in methanol and DCM with a gradient of 0-15% to give methyl (1aR,7bS)-5-[2-(1-ethylpiperidin-3-ylmethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (0.071 g).

^{1}H NMR ($CDCl_3$) δ: 7.95-7.88 (1H, m), 7.21-7.15 (1H, m), 7.03-6.86 (3H, m), 4.31 (1H, d), 3.81-3.73 (4H, m), 2.89-2.63 (4H, m), 2.39-2.28 (2H, m), 2.09-2.08-1.95 (1H, m), 1.94-1.44 (8H, m), 1.06-0.94 (6H, m).

Intermediate 222

2-(1-Ethylpiperidin-3-ylmethyl)-4-fluoro-benzene-sulfonyl chloride

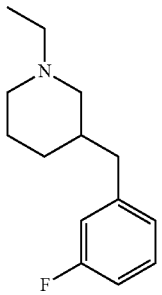


A solution of 1-ethyl-3-(3-fluorobenzyl)piperidine (Intermediate 223, 0.214 g) in DCE (1 mL) was added to chlorosulfonic acid (2 mL) at 0° C. The mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was added dropwise to a mixture of ice and brine and extracted with DCM. The organic layer was dried (Na_2SO_4) and filtered and the filtrate was evaporated to dryness to give 2-(1-ethylpiperidin-4-ylmethyl)-4-fluorobenzene-sulfonyl chloride (0.44 g) as a solid.

^{1}H NMR ($CDCl_3$) δ: 8.17-8.11 (1H, m), 7.43-7.37 (1H, m), 7.19-7.12 (1H, m), 3.62-3.52 (1H, m), 3.42-3.32 (1H, m), 3.16 (2H, d), 3.11-2.92 (3H, m), 2.64-2.29 (3H, m), 1.91 (2H, d), 1.43 (3H, t), 1.39-1.23 (1H, m).

Intermediate 223

1-Ethyl-3-(3-fluorobenzyl)-piperidine

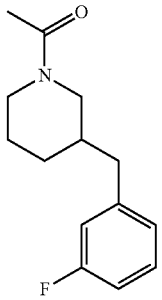


A solution of lithium aluminium hydride (2M in THF, 2.8 mL) was added dropwise to a solution of 1-[3-(3-fluorobenzyl)piperidin-1-yl]ethanone (Intermediate 224, 0.66 g) in anhydrous THF (20 mL) at 0° C. under argon. The mixture was stirred for 30 minutes then allowed to warm to room temperature and stirred for 2 hours. The mixture was recooled to 0° C. and water was added. The mixture was extracted with ether, washed with brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness to give 1-ethyl-3-(3-fluorobenzyl)piperidine (0.535 g).

^{1}H NMR ($CDCl_3$) δ: 7.25-7.17 (1H, m), 6.95-6.80 (3H, m), 2.92-2.73 (2H, m), 2.58-2.42 (2H, m), 2.42-2.26 (2H, m), 1.96-1.76 (2H, m), 1.74-1.48 (4H, m), 1.04 (3H, t), 1.00-0.84 (1H, m).

Intermediate 224

1-[3-(3-Fluorobenzyl)piperidin-1-yl]ethanone

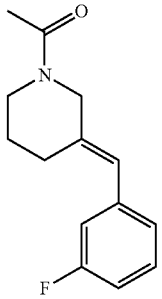


A mixture of 1-{3-[1-(3-fluorophenyl)methylidene]piperidin-1-yl}ethanone (Intermediate 225, 0.7 g), palladium hydroxide (20% on carbon, 0.07 g) in ethyl acetate (20 mL) and IMS (1 mL) was degassed by nitrogen/vacuum purging. The mixture was stirred under an atmosphere of hydrogen for 21.5 hours. The mixture was filtered the filtrate was evaporated to dryness to give 1-[3-(3-fluorobenzyl)piperidin-1-yl]ethanone (0.66 g).

^{1}H NMR ($CDCl_3$) δ: 7.31-7.17 (1H, m), 6.97-6.80 (3H, m), 4.52-4.43 (0.5H, m), 4.41-4.31 (0.5H, m), 3.76-3.65 (0.5H, m), 3.65-3.55 (0.5H, m), 3.07-2.95 (0.5H, m), 2.82-2.62 (1.5H, m), 2.60-2.49 (1H, m), 2.45-2.33 (1H, m), 2.08 (1.5H, s), 1.95 (1.5H, s), 1.83-1.63 (3H, m), 1.50-1.32 (1H, m), 1.29-1.09 (1H, m).

Intermediate 225

1-{3-[1-(3-Fluorophenyl)methylidene]piperidin-1-yl}ethanone



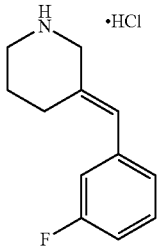
Acetyl chloride (0.515 mL) was added to a mixture of 3-[1-(3-fluorophenyl)methylidene]-piperidine hydrochloride (Intermediate 226, 1.5 g) and N,N-di-isopropyl-N-ethylamine (2.52 mL) in anhydrous THF (50 mL) at 0° C. under nitrogen. The mixture was allowed to warm to room temperature and was stirred for 2 hours. The mixture was diluted with water (100 mL) and extracted with ether, washed with brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on

silica eluting with a mixture of ethyl acetate and cyclohexane with a gradient of 75-100% to give 1-{3-[1-(3-fluorophenyl)-methylidene]piperidin-1-yl}ethanone (1.38 g).

^{1}H NMR ($CDCl_3$) δ: 7.37-7.21 (1H, m), 7.04-6.82 (3H, m), 6.48-6.26 (1H, 4s), 4.39-4.00 (2H, m), 3.72-3.48 (2H, m), 2.61-2.41 (2H, m), 2.18-2.02 (3H, 4s), 1.83-1.61 (2H, m).

Intermediate 226

3-[1-(3-Fluorophenyl)methylidene]piperidine hydrochloride

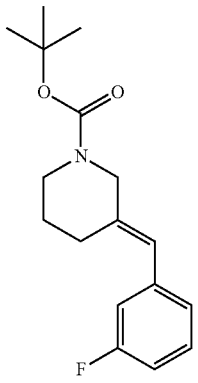


A solution of HCl in dioxane (4M, 30 mL) was added to a solution of tert-butyl 3-[1-(3-fluorophenyl)methylidene]piperidine-1-carboxylate (Intermediate 227, 2.38 g) in ether (30 mL) and the mixture was stirred at room temperature for 5 hours. The mixture was concentrated in vacuo and the residue was treated with ether. The solid was collected by filtration, washed with ether and dried under vacuum to give 3-[1-(3-fluorophenyl)methylidene]piperidine hydrochloride (1.64 g).

^{1}H NMR ($CDCl_3$) δ: 2 ratio of E and Z isomers δ: 9.34 (2H, br s), 7.48-7.37 (1H, m), 7.22-7.00 (3H, m), 6.59 (1H, s), 3.78-3.68 (2H, m), 3.13 (2H, m), 2.52 (1.2H, m), 2.43 (0.8H, m), 1.84 (1.2H, m), 1.76 (0.8H, m).

Intermediate 227

tert-Butyl 3-[1-(3-fluorophenyl)methylidene]piperidine-1-carboxylate

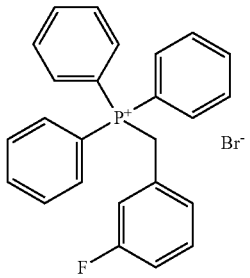


(3-Fluorobenzyltriphenylphosphonium bromide (Intermediate 228, 5.3 g) was added in portions to a solution of sodium tert-butoxide (1.06 g) in anhydrous THF (20 mL) at room temperature and the mixture was stirred for 30 minutes. A solution of tert-butyl 3-oxopiperidine-1-carboxylate (2 g) in anhydrous THF (10 mL) was added dropwise at room temperature and the mixture was stirred for 24 hours. The mixture was diluted with water (100 mL) and extracted with ether (100 mL), washed with brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography on silica eluting with a mixture of ethyl acetate and cyclohexxane with a gradient of 0-20% to give tert-butyl 3-[1-(3-fluorophenyl)-methylidene]piperidine-1-carboxylate (1.42 g).

^{1}H NMR ($CDCl_3$) δ: 2 ratio of E and Z isomers δ: 7.33-7.21 (1H, m), 7.05-6.85 (3H, m), 6.37 (0.6H, s), 6.28 (0.4H, s), 4.16 (0.8H, s), 4.00 (1.2H, s), 3.50 (2H, t), 2.50 (1.2H, m), 2.39 (0.8H, m), 1.72 (0.8H, m), 1.62 (1.2H, m), 1.48 (5.4H, s), 1.34 (3.6H, br s).

Intermediate 228

(3-Fluorobenzyl)triphenylphosphonium bromide

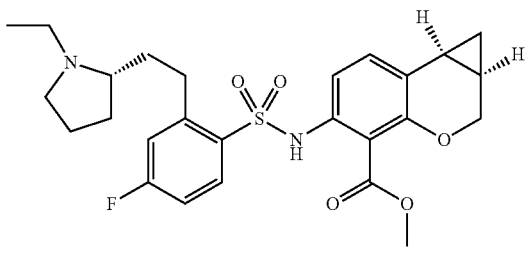


A mixture of 3-fluorobenzyl bromide (5 g) and triphenyl phosphine (6.94 g) in toluene (50 mL) was heated at reflux for 3 hours. After cooling, the solid was collected by filtration, washed with toluene and dried under vacuum at 50° C. to give (3-fluorobenzyl)triphenylphosphonium bromide (10.1 g).

^{1}H NMR (DMSO-d_6) δ: 7.96-7.87 (3H, m), 7.81-7.64 (12H, m), 7.35-7.26 (1H, m), 7.20-7.11 (1H, m), 6.88-6.82 (1H, m), 6.78-6.70 (1H, m), 5.21 (2H, d).

Intermediate 229

Methyl (1aR,7bS)-5-{2-[2-((R)-1-ethylpyrrolidin-2-yl)ethyl]-4-fluoro-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate

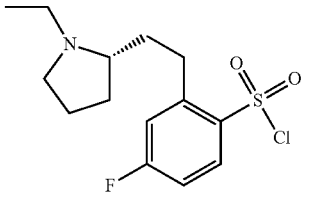


Prepared by proceeding in a similar manner to Intermediate 95, starting from 2-[2-((R)-1-ethyl-pyrrolidin-2-yl)-ethyl]-4-fluorobenzenesulfonyl chloride (intermediate 230) and methyl (1aR,7bS)-5-amino-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylate (Intermediate 42A).

LCMS (Method A) r/t 2.30 (M+H) 503.

Intermediate 230

2-[2-((R)-1-Ethylpyrrolidin-2-yl)ethyl]-4-fluorobenzenesulfonyl chloride

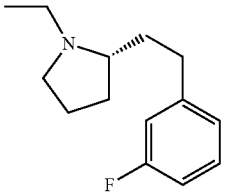


Prepared by proceeding in a similar manner to intermediate 96, starting from (R)-1-ethyl-2-[2-(3-fluorophenyl)ethyl] pyrrolidine (intermediate 231).

^{1}H NMR ($CDCl_3$) δ: 8.11 (1H, dd), 7.42 (1H, dd), 7.14 (1H, t), 3.93 (1H, m), 3.46-3.21 (2H, m), 3.13 (1H, m), 2.91 (2H, m), 2.43 (2H, m), 2.32 (2H, m), 2.11 (3H, m), 1.50 (3H, t).

Intermediate 231

(R)-1-Ethyl-2-[2-(3-fluorophenyl)ethyl]pyrrolidine

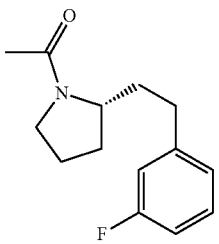


A solution of 1-{(R)-2-[2-(3-fluorophenyl)ethyl]pyrrolidin-1-yl}ethanone (Intermediate 232, 0.48 g) in THF (20 mL) was cooled to 0° C. and treated with a solution of lithium aluminum hydride (2M in THF, 3.6 mL) under an atmosphere of nitrogen. The resultant mixture was allowed to warm to room temperature before heating to 60° C. overnight. The mixture was cooled to 0° C. and treated with water (0.35 ml), 4N sodium hydroxide solution (0.35 ml) and further water (0.9 ml). Sodium bisulphate powder was added to the suspension and the slurry was filtered through Celite and the filtrate was evaporated to dryness to give (R)-1-ethyl-2-[2-(3-fluorophenyl)ethyl]pyrrolidine (0.41 g) as an oil.

^{1}H NMR ($CDCl_3$) δ: 7.22 (1H, m), 6.96 (1H, d), 6.87 (2H, m), 3.18 (1H, dd), 2.87 (1H, m), 2.69 (1H, m), 2.55 (1H, m), 2.20 (1H, dq), 2.12-1.91 (4H, m), 1.75 (2H, m), 1.54 (2H, m), 1.10 (3H, t). HNMR 205205

Intermediate 232

1-{(R)-2-[2-(3-Fluorophenyl)ethyl]pyrrolidin-1-yl}ethanone

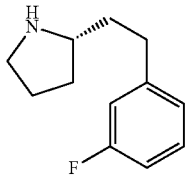


Acetyl chloride (0.29 ml) was added to a solution of N,N-diisopropyl-N-ethylamine (0.71 ml) and (R)-2-[2-(3-fluorophenyl)ethyl]-pyrrolidine (Intermediate 233, 0.39 g) in DCM (30 ml) and the mixture was stirred for 1.5 hours. The mixture was washed with 1M HCl, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give 1-{(R)-2-[2-(3-fluorophenyl)ethyl]-pyrrolidin-1-yl}ethanone (0.48 g) as an oil.

^{1}H NMR (d_6-DMSO, 80° C.) δ: 7.28 (1H, q), 7.02 (2H, t), 6.92 (1H, t), 3.93 (1H, br s), 3.41 (2H, m), 2.60 (2H, m), 2.05-1.54 (6H, m), 1.90 (3H, t).

Intermediate 233

(R)-2-[2-(3-Fluorophenyl)ethyl]pyrrolidine

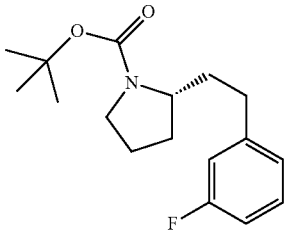


Trifluoroacetic acid (5 mL) was added to a solution of tert-butyl (R)-2-[2-(3-fluorophenyl)ethyl]-pyrrolidine-1-carboxylate (Intermediate 234, 0.55 g) in DCM (5 mL) and the mixture was stirred at room temperature for 1.5 hours. The mixture was evaporated to dryness and the residue was dissolved in a small amount of methanol and loaded onto a 20 g SCX-2 SPE cartridge, washed with methanol then eluted with 2M ammonia in methanol to give (R)-2-[2-(3-fluorophenyl)-ethyl]pyrrolidine (0.39 g).

^{1}H NMR ($CDCl_3$) δ: 7.23 (1H, q), 6.97 (1H, d), 6.88 (2H, m), 2.99 (2H, m), 2.85 (1H, m), 2.69 (2H, m), 1.91 (1H, m), 1.75 (3H, m), 1.61 (1H, br s), 1.28 (1H, m).

Intermediate 234

tert-Butyl (R)-2-[2-(3-fluorophenyl)ethyl]pyrrolidine-1-carboxylate



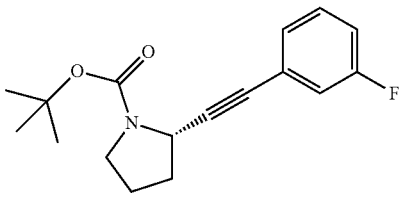
A solution of tert-butyl (S)-2-(3-fluorophenylethynyl)pyrrolidine-1-carboxylate (Intermediate 235, 1.26 g) in IMS (70 mL) was carefully added to 20% palladium on carbon (0.6 g) under a carbon dioxide atmosphere. The mixture was degassed under vacuum and placed under an atmosphere of hydrogen. This was repeated three times then the mixture was stirred under an atmosphere of hydrogen for 18 hours. The mixture was filtered through Celite and the filtrate was evaporated to dryness. The residue was purified by chromatography on silica, eluting with a mixture of DCM and pentane with a

gradient of 0-100% to give tert-butyl (R)-2-[2-(3-fluoro-phenyl)ethyl]pyrrolidine-1-carboxylate (0.55 g) as an oil.

^{1}H NMR ($CDCl_3$) δ: 7.21 (1H, br m), 6.99-6.81 (3H, br m), 3.80 (1H, br d), 3.37 (2H, br d), 2.61 (2H, br m), 1.97 (2H, br m), 1.83 (2H, m), 1.65 (2H, br m), 1.45 (9H, s).

Intermediate 235

tert-Butyl (S)-2-(3-fluorophenylethynyl)pyrrolidine-1-carboxylate

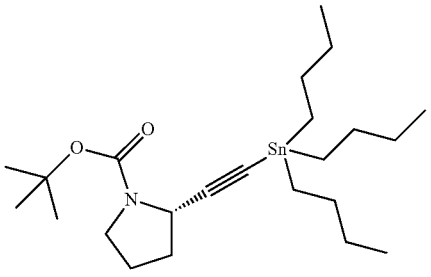


A suspension of 3-fluorobromobenzene (0.62 ml), tris (dibenzylideneacetone)dipalladium(0) (0.276 g), tri-tert-butylphosphonium tetrafluoroborate (0.165 g) and tert-butyl (S)-2-tributyl-stannanylethynylpyrrolidine-1-carboxylate (Intermediate 236, 2.94 g) in anhydrous toluene (40 ml) was degassed under nitrogen and stirred at room temperature for 1.5 hours. The mixture was evaporated to dymess and the residue was purified by chromatography on silica, eluting with a mixture of DCM and pentane with a gradient of 0-100% to give tert-butyl (S)-2-(3-fluoro-phenylethynyl)pyrrolidine-1-carboxylate (1.26 g) as an oil.

^{1}H NMR ($CDCl_3$) δ: 7.25 (1H, m), 7.16 (1H, br d), 7.08 (1H, br d), 6.99 (1H, br t), 4.69 (1H, br d), 3.51 (1H, br s), 3.37 (1H, br s), 2.11 (3H, br m), 1.94 (1H, br s), 1.49 (9H, s).

Intermediate 236

tert-Butyl(S)-2-tributylstannanylethynylpyrrolidine-1-carboxylate



n-Butyl lithium (2.5M solution in hexanes. 11 mL) was added dropwise to a cooled solution of tert-butyl (S)-2-ethynylpyrrolidine-1-carboxylate (prepared according A Paul et al, *Tetrahedron,* 2006, 62, 8919, 4.49 g) in dry THF (230 ml) under an atmosphere of nitrogen while maintaining the temperature below −65° C. When the addition was completed, the mixture was stirred at −78° C. for 15 minutes then allowed to warm to 0° C. and stirred for 2.5 hours. Tributyl tin chloride (7.7 mL) was added dropwise over five minutes and the mixture was stirred at room temperature for 1.5 hours. The mixture was cooled to 0° C. and saturated sodium bicarbonate was added while maintaining the temperature below 15° C. The layers were separated and the aqueous layer was extracted with ethyl acetate, washed with saturated sodium bicarbonate, water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica, eluting with a mixture of pentane and ethyl acetate with a gradient of 0-7.5% to give tert-butyl (S)-2-tributylstannanylethynylpyrrolidine-1-carboxylate (0.39 g) as an oil.

^{1}H NMR ($CDCl_3$) δ: 4.41 (1H, br s), 3.45 (1H, br m), 3.28 (1H, br s), 2.03 (3H, br m), 1.86 (1H, br s), 1.54 (6H, m), 1.48 (9H, s), 1.33 (6H, q), 0.95 (6H, t), 0.90 (9H, t).

Biological Example:

Compounds are tested for their capacity to inhibit recombinant human MetAP2 activity using the following assay.

Human recombinant MetAP2 expressed in Sf9 cells followed by affinity purification and EDTA treatment to remove endogenous active site cation was dialysed against $MnCl_2$ to produce the manganese enzyme used in the assay. The assay was carried out for 30 minutes at 25° C. in 50 mM HEPES buffer containing 100 mM NaCl, pH 7.5 the presence of 0.75 mM Methionine-Alanine-Serine (MAS) substrate and 50 μg/ml amino acid oxidase using a dilution of purified MetAP2 giving >3-fold signal:noise. Cleavage of the substrate by MetAP2 and oxidation of free methionine by amino acid oxidase was detected and quantified using fluorescence generated by Amplex red (10-acetyl-3,7-dihydroxyphenoxazine) in combination with horseradish peroxidase which detects H_2O_2 released during the oxidation step. The fluorescent signal was detected using a multiwell fluorimeter. Compounds were diluted in DMSO prior to addition to assay buffer, the final DMSO concentration in the assay being 1%.

The IC_{50} is defined as the concentration at which a given compound achieves 50% inhibition of control. IC_{50} values are calculated using the XLfit software package (version 2.0.5).

Compounds of the invention demonstrated activity in the assay of this Example as indicated in the following table, wherein A represents <0.05 μM, B represents IC_{50} between 0.05 μM and 0.5 μM, and C represents IC_{50}>0.5 μM.

Compound name	Activity
Cis-(3aRS,9bRS)-7-(Benzenesulfonylamino)-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid	B
Cis-(3aRS,9bRS)-7-[2-(3-Diethylaminopropyl)-4-fluorobenzenesulfonyl-amino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid	B
Cis-(3aRS,9bRS)-7-[2-(3-{Pyrrolidin-1-yl}propyl)-4-fluorobenzene-sulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid	A
Cis-(3aRS,9bRS)-7-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluoro-benzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid	A
First eluting enantiomer of cis-(3aRS,9bRS)-7-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluoro-benzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid	A
Second eluting enantiomer of cis-(3aRS,9bRS)-7-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluoro-benzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid	B
7-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,2-dihydrofuro[2,3-c]quinoline-6-carboxylic acid formate salt	A
7-(Benzenesulfonylamino))-1,2-dihydrofuro[2,3-c]quinoline-6-carboxylic acid formate salt	A
Cis-(3aRS,9bRS)-7-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,2,3a,4,5,9b-hexahydrofuro[2,3-c]quinoline-6-carboxylic acid	A
5-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A

-continued

Compound name	Activity
(1aS,7bR) 5-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aR,7bS) 5-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-[2-((E)-3-Diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
Cis-(3aRS,9bRS)-7-[2-(4-dimethylamino-butylamino)-benzenesulfonylamino]-1,3a,4,9b-tetrahydro-2H-furo[2,3-c]chromene-6-carboxylic acid	B
(1aR,7bS)-5-[2-(3-Diethylaminopropyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-[2-((Z)-3-Diethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
First eluting enantiomer of (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
Second eluting enantiomer of (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-[2((Z)-3-Ethylaminoprop-1-enyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	A
First eluting enantiomer of (1aRS,7bSR)-5-[2((Z)-3-ethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
Second eluting enantiomer of (1aRS,7bSR)-5-[2((Z)-3-ethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2[(Z)-3-(Pyrrolidin-1-yl)prop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid	A
First eluting enantiomer of (1aRS,7bSR)-5-{2[(Z)-3-(pyrrolidin-1-yl)prop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid	B
Second eluting enantiomer of (1aRS,7bSR)-5-{2[(Z)-3-(pyrrolidin-1-yl)prop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-[2-(3-Dimethylaminopropylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
First eluting enantiomer of (1aRS,7bSR)-5-[2-(3-dimethylaminopropylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	C
Second eluting enantiomer of (1aRS,7bSR)-5-[2-(3-dimethylaminopropylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-[2-(4-Dimethylaminobutylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
First eluting enantiomer of (1aRS,7bSR)-5-[2-(4-dimethylaminobutylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
Second eluting enantiomer of (1aRS,7bSR)-5-[2-(4-dimethylaminobutylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-[2-(5-Dimethylaminopentylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-{2[(Z)-3-(propan-2-yl)aminoprop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2[(Z)-3-((S)-3-hydroxypyrrolidin-1-yl)aminoprop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B

-continued

Compound name	Activity
(1aRS,7bSR)-5-{2[(Z)-3-((R)-3-Hydroxypyrrolidin-1-yl)aminoprop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-[2((Z)-4-Diethylaminobut-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
First eluting enantiomer of (1aRS,7bSR)-5-[2((Z)-4-diethylaminobut-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
Second eluting enantiomer of (1aRS,7bSR)-5-[2((Z)-4-diethylaminobut-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[2-(4-Ethylpiperazin-1-yl)-ethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2[(Z)-3-(Azetidin-1-yl)prop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2[(Z)-3-(3-Hydroxyazetidin-1-yl)prop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-{2[(Z)-3-(Azetidin-1-yl)propyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-[2((Z)-4-Diethylaminobutyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[N-(4-Dimethylaminobutyl)-N-methylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	C
(1aRS,7bSR)-5-{2-[((S)-1-Ethylpyrrolidin-3-ylcarbamoyl)-methyl]-4-fluoro-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-[2-(1-Ethylazetidin-3-yl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[((R)-1-Ethylpyrrolidin-3-ylcarbamoyl)-methyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[2-(Pyrrolidin-1-yl)-ethyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-[2-((R)-1-Ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid	A
First eluting enantiomer of (1aRS,7bSR)-5-[2-((R)-1-ethyl-pyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid	B
Second eluting enantiomer of (1aRS,7bSR)-5-[2-((R)-1-Ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-{2-[((S)-1-Ethylpyrrolidin-2-yl)cabonyl-aminomethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-[2-(4-Dimethylaminobutyrylamino)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-[2-((S)-1-Ethyl-pyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-[2-(3-Dimethylaminopropylcarbamoyl)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-(2-{[N-((S)-1-Ethyl-pyrrolidin-3-yl)-N-methyl-carbamoyl]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-(2-{[N-((R)-1-Ethylpyrrolidin-3-yl)-N-methyl-carbamoyl]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[2-((S)-1-Ethylpyrrolidin-2-yl)ethylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	A

-continued

Compound name	Activity
(1aRS,7bSR)-5-{2-[2-((R)-1-Ethylpyrrolidin-2-yl)ethylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-[2-(3-N,N,-Diethylaminopropylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-(2-{[((R)-1-Ethylpyrrolidine-2-yl)carbonyl-amino]methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[(1-Ethylazetidin-3-ylmethyl)amino]benzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
First eluting enantiomer of (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
Second eluting enantiomer of (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-(2-{N-[((R)-1-Ethylpyrrolidine-2-yl)carbonyl]-N-methylaminomethyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-(2-{N-[((S)-1-Ethylpyrrolidine-2-yl)carbonyl]-N-methylamino-methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-[2-(4-Dimethylaminobutylamino)-4-fluoro-benzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[((R)-1-Ethylpyrrolidin-3-ylmethyl)amino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[((S)-1-Ethylpyrrolidin-3-ylmethyl)amino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-[2-(4-Ethyl-2-oxopiperazin-1-ylmethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-[2-(1-Ethylpiperidin-4-ylmethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-{2-[2-(1-Ethylazetidin-3-yl)ethyl]-4-fluoro-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[((S)-1-Azabicyclo[2.2.2]oct-3-yl)amino]benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[((R)-1-Azabicyclo[2.2.2]oct-3-yl)amino]benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-(2-{[((S)-1-ethylpyrrolidine-3-carbonyl)amino]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[2-((R)-1-Ethylpyrrolidin-3-ylamino)ethyl]-4-fluoro-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[((R)-1-Ethylpyrrolidin-3-yl)amino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[((S)-1-Ethylpyrrolidin-3-yl)amino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-(2-{[((R)-1-Ethylpyrrolidine-3-carbonyl)amino]-methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-[2-((Z)-3-Diethylamino-2-methylprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	A
(1aRS,7bSR)-5-{2-[2-((R)-1-Ethylpyrrolidin-3-yl)ethylamino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aRS,7bSR)-5-{2-[2-((S)-1-Ethylpyrrolidin-3-yl)ethylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aR,7bS)-5-[2-((S)-1-Ethylpyrrolidin-3-yloxymethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B

-continued

Compound name	Activity
(1aR,7bS)-5-[2-((R)-1-Ethylpyrrolidin-3-yloxymethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B
(1aR,7bS)-5-[2-(1-Ethylpiperidin-3-ylmethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid	B
(1aR,7bS)-5-{2-[2-((R)-1-Ethylpyrrolidin-2-yl)ethyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid	B

INCORPORATION BY REFERENCE

All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety for all purposes as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

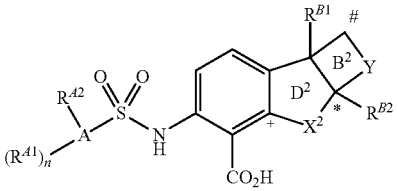
While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention.

What is claimed is:

1. A tricyclic compound represented by:

Formula II



wherein:

the ring B^2 is optionally substituted by one or more fluorine atoms on any of the available carbon atoms;

B^2 is fused to ring D^2 such that the two atoms shared by B^2 and D^2 are both carbon;

X^2 is $^+$—W^2—$C(R^{D5}R^{D6})$—*; wherein the + and * indicate the attachment points of X^2 as indicated in Formula II;

Y is a bond; wherein the * and # indicate the attachment points of Y as indicated in Formula II;

W^2 is O;

A is phenyl;

R^{B1} and R^{B2} are independently selected from the group consisting of H, F, OH, CN, C_{1-2}alkoxy or C_{1-3}alkyl;

wherein C_{1-3}alkyl and C_{1-2}alkoxy are optionally substituted by a group selected from OH, C_{1-2}alkoxy, CN or one or more fluorine atoms;

R^{A1} is selected, independently for each occurrence, from the group consisting of hydrogen, hydroxyl, cyano, halogen, C_{1-4}alkyl or C_{1-3}alkoxy; wherein or C_{1-3}alkoxy may be optionally substituted by one or more fluorines;

n is 0, 1, or 2;

R^{A2} is selected from the group consisting of hydrogen, R^iR^jN—, heterocyclyl, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy; wherein said heterocyclyl may optionally be substituted by one or more groups R^g; and wherein if said heterocyclyl contains a —NH moiety, that nitrogen may optionally be substituted by one or more groups R^h; and wherein said C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}cycloalkyl and C_{1-6}alkoxy may optionally be substituted by one or more groups R^P;

R^{D5} and R^{D6} are each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorine atoms, cyano, hydroxyl or $N(R^aR^b)$;

R^a and R^b are independently selected, for each occurrence, from the group consisting of hydrogen and C_{1-3}alkyl; wherein C_{1-3}alkyl may optionally be substituted by one or more substituents selected from fluorine, cyano, oxo and hydroxyl;

or R^a and R^b, together with the nitrogen to which they are attached, may form a 4-6 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-6 membered heterocyclic ring may optionally be substituted by one or more substituents selected from the group consisting of fluorine, cyano, oxo or hydroxyl;

R^g is independently selected for each occurrence from the group consisting of R^P, hydrogen, oxo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, (wherein w is 0, 1 or 2), C_{1-6}alkyl-carbonyl-$N(R^a)$— and C_{1-6}alkoxycarbonyl-$N(R^a)$—; wherein C_{1-6}alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy may be optionally substituted by one or more substituents selected from R^P;

R^h is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$—, C_{1-6}alkoxycarbonyl-, R^iR^jN-carbonyl- and R^iR^jN—SO_2—; wherein C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl may optionally be substituted by one or more substituents selected from R^P;

R^i and R^j are selected independently for each occurrence from the group consisting of hydrogen, C_{1-4}alkyl C_{3-6}cycloalkyl, heterocyclyl and heterocyclylcarbonyl; wherein C_{1-4}alkyl and C_{3-6}cycloalkyl may be optionally substituted by one or more substituents selected from fluorine, hydroxyl, cyano, R^aR^bN—, R^aR^bN-carbonyl- and C_{1-3}alkoxy and wherein heterocyclyl and heterocyclylcarbonyl may be optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, halo-C_{1-6}-alkyl, hydroxyl-C_{1-6}-alkyl, R^aR^bN—C_{1-6}alkyl- and C_{1-6}-alkoxy-C_{1-6}-alkyl group; and wherein if said heterocyclyl or heterocyclylcarbonyl contains a —NH moiety that nitrogen may optionally be substituted by one or more groups C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$— and C_{1-6}-alkylcarbonyl; or R^i and R^j taken together with the nitrogen to which they are attached form a 4-7 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-7 membered heterocyclic ring may be optionally substituted on carbon by one or more substituents selected from the group consisting of fluorine, hydroxyl, oxo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, R^aR^bN—, R^aR^bN—SO_2— and R^aR^bN-carbonyl-; wherein said C_{1-6}alkyl or C_{1-6}alkoxy may optionally be substituted by fluorine, hydroxyl or cyano; and wherein the 4-7 membered heterocyclic ring may be optionally substituted on nitrogen by one or more substituents selected from the group consisting of C_{1-6}alkyl and R^aR^bN-carbonyl-; and wherein said C_{1-6}alkyl may be optionally substituted by one or more substituents selected from the group consisting of fluorine, hydroxyl, cyano;

R^P is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, cyano, C_{1-6}alkoxy, R^iR^jN—, R^iR^jN-carbonyl-, R^iR^jN—SO_2— and R^iR^jN-carbonyl-$N(R^a)$—;

and pharmaceutically acceptable salts, and stereoisomers thereof.

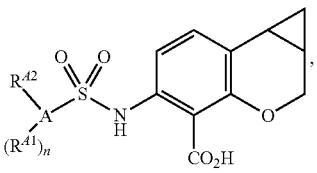
2. The tricyclic compound of claim **1**, wherein R^{D5} and R^{D6} are independently selected for each occurrence from the group consisting of hydrogen, fluorine, cyano and C_{1-2}alkyl.

3. The tricyclic compound of claim **2**, wherein R^{D5} and R^{D6} are hydrogen.

4. The tricyclic compound of claim **1**, wherein R^{B1} is selected from the group consisting of H, F and C_{1-2}alkyl.

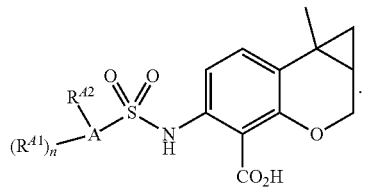
5. The tricyclic compound of claim **1**, wherein the compound is represented by:

Ib



and

Ig

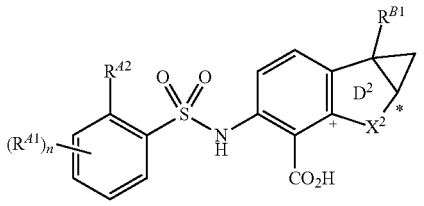


6. The tricyclic compound of claim **1**, wherein R^{A1} is selected from the group consisting of hydrogen, halogen, C_{1-2}alkyl and C_{1-2}alkoxy; wherein C_{1-2}alkyl may optionally be substituted by one or more fluorines.

7. The tricyclic compound of claim **1**, wherein R^{A2} is selected from the group consisting of 3-(N,N-diethylamino) propyl, 3-(pyrrolidin-1-yl)propyl, (Z)-3-(N,N-diethylamino) prop-1-enyl, (Z)-3-(azetidin-1-yl)prop-1-enyl and (Z)-3-(pyrrolidin-1-yl)prop-1-enyl.

8. The tricyclic compound represented by:

Formula IV



D^2 is partially unsaturated heterocyclic ring wherein X^2 is $^+$—W^2—$C(R^{D5}R^{D6})$—*; wherein the $^+$ and * indicate the attachment points of X^2 as indicated in Formula IV;

W^2 is O;

R^{B1} is selected from the group consisting of H, F, OH, CN, C_{1-2}alkoxy or C_{1-3}alkyl; wherein C_{1-3}alkyl and C_{1-2}alkoxy are optionally substituted by a group selected from OH, C_{1-2}alkoxy, CN or one or more fluorine atoms;

R^{A1} is selected, independently for each occurrence, from the group consisting of hydrogen, hydroxyl, cyano, halogen, C_{1-4}alkyl or C_{1-3}alkoxy; wherein C_{1-4}alkyl, or C_{1-3}alkoxy may be optionally substituted by one or more fluorines;

n is 0, 1, or 2;

R^{A2} is selected from the group consisting of hydrogen, R^iR^jN—, heterocyclyl, heterocyclyloxy and heterocyclyl-(NR^a)—; wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g and wherein if said heterocyclyl contains a —NH moiety that nitrogen may optionally be substituted by one or more groups R^h; or

R^{A2} is selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl-$S(O)_w$— (wherein w is 0, 1 or 2), C_{1-6}alkyl-N(R^a)—, C_{1-6}alkyl-N(R^a)-carbonyl-, C_{1-6}alkylcarbonyl-N(R^a)—, C_{1-6}alkyl-N(R^a)-carbonyl-N(R^a)—, C_{1-6}alkyl-N(R^a)—SO_2—, C_{1-6}alkyl-SO_2—N(R^a)—, C_{1-6}alkoxycarbonyl-N(R^a)—, C_{1-6}alkylcarbonyl-N(R^a)—C_{1-6}alkyl-, C_{1-6}alkyl-N(R^a)-carbonyl-C_{1-6}alkyl-, C_{1-6}alkoxyC_{1-6}alkyl-; (wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, and C_{3-6}cycloalkoxy, may optionally be substituted by R^P), heterocyclyl, heterocyclyloxy or heterocyclyl-N(R^a)—; (wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g; and wherein if said heterocyclyl contains a —NH moiety that nitrogen may optionally be substituted by one or more groups R^h);

R^{D5} and R^{D6} are each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorine atoms, cyano, hydroxyl or $N(R^aR^b)$;

R^a and R^b are independently selected, for each occurrence, from the group consisting of hydrogen and C_{1-3}alkyl; wherein C_{1-3}alkyl may optionally be substituted by one or more substituents selected from fluorine, cyano, oxo and hydroxyl;

or R^a and R^b, together with the nitrogen to which they are attached, may form a 4-6 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-6 membered heterocyclic ring may optionally be substituted by one or more substituents selected from the group consisting of fluorine, cyano, oxo or hydroxyl;

R^g is independently selected for each occurrence from the group consisting of R^P, hydrogen, oxo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$—, (wherein w is 0, 1 or 2), C_{1-6}alkyl-carbonyl-N(R^a)— and C_{1-6}alkoxycarbonyl-N(R^a)—; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, may be optionally substituted by one or more substituents selected from R^P;

R^h is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$—, C_{1-6}alkoxycarbonyl-, R^iR^jN-carbonyl- and R^iR^jN—SO_2—; wherein C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, and C_{3-6}cycloalkyl may optionally be substituted by one or more substituents selected from R^P;

R^i and R^j are selected independently for each occurrence from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, heterocyclyl and heterocyclylcarbonyl; wherein C_{1-4}alkyl and C_{3-6}cycloalkyl may be optionally substituted by one or more substituents selected from fluorine, hydroxyl, cyano, R^aR^bN—, R^aR^bN-carbonyl- and C_{1-3}alkoxy and wherein heterocyclyl and heterocyclylcarbonyl may be optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, halo-C_{1-6}-alkyl, hydroxyl-C_{1-6}-alkyl, R^aR^bN—C_{1-6}alkyl- and C_{1-6}-alkoxy-C_{1-6}-alkyl group; and wherein if said heterocyclyl or heterocyclylcarbonyl contains a —NH moiety that nitrogen may optionally be substituted by one or more groups C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$— and C_{1-6}-alkylcarbonyl; or R^i and R^j taken together with the nitrogen to which they are attached form a 4-7 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-7 membered heterocyclic ring may be optionally substituted on carbon by one or more substituents selected from the group consisting of fluorine, hydroxyl, oxo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, R^aR^bN—, R^aR^bN—SO_2— and R^aR^bN-carbonyl-; wherein said C_{1-6}alkyl or C_{1-6}alkoxy may optionally be substituted by fluorine, hydroxyl or cyano; and wherein the 4-7 membered heterocyclic ring may be optionally substituted on nitrogen by one or more substituents selected from the group consisting of C_{1-6}alkyl and R^aR^bN-carbonyl-; and wherein said C_{1-6}alkyl may be optionally substituted by one or more substituents selected from the group consisting of fluorine, hydroxyl, cyano;

R^P is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, cyano, C_{1-6}alkoxy, R^iR^jN-carbonyl-, R^iR^jN—SO_2— and R^iR^jN-carbonyl-N(R^a)—;

and a pharmaceutically acceptable salt or stereoisomer thereof.

9. The tricyclic compound of claim 8, wherein R^{A1} is selected from hydrogen or fluorine.

10. The tricyclic compound of claim 8, wherein R^{A2} is selected from the group consisting of hydrogen, R^iR^jN, heterocyclyl, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy; wherein said heterocyclyl may optionally be substituted by one or more groups R^g; and wherein if said heterocyclyl contains a —NH moiety, that nitrogen may option-

ally be substituted by one or more groups R^h; and wherein said C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}cycloalkyl and C_{1-6}alkoxy may optionally be substituted by one or more groups R^p.

11. A compound selected from the group consisting of: (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-((E)-3-diethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-7b-methyl-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-(3-diethylaminopropyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1-difluoro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2((Z)-3-ethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2((Z)-3-ethylaminoprop-1-enyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2((Z)-3-ethylaminoprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-(pyrrolidin-1-yl)prop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-{2[(Z)-3-(pyrrolidin-1-yl)prop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-{2[(Z)-3-(pyrrolidin-1-yl)prop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(3-dimethylamino-propylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-(3-dimethylaminopropylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2-(3-dimethylamino-propylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(4-dimethylaminobutylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-(4-dimethylaminobutyl-amino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2-(4-dimethylaminobutylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(5-dimethylamino-pentylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-(propan-2-yl)aminoprop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-((S)-3-hydroxypyrrolidin-1-yl)aminoprop-1-enyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-((R)-3-hydroxypyrrolidin-1-yl)aminoprop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2((Z)-4-diethylaminobut-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2((Z)-4-diethylaminobut-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2((Z)-4-diethylaminobut-1-enyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-(4-ethylpiperazin-1-yl)-ethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-(azetidin-1-yl)prop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-(3-hydroxyazetidin-1-yl)prop-1-enyl]-4-fluorobenzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2[(Z)-3-(azetidin-1-yl)propyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2((Z)-4-diethylaminobutyl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[N-(4-dimethylamino-butyl)-N-methylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-3-ylcarbamoyl)methyl]-4-fluoro-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(1-ethylazetidin-3-yl)-4-fluorobenzenesulfonylamino]-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((R)-1-ethylpyrrolidin-3-ylcarbamoyl)methyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydro-cyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-(pyrrolidin-1-yl)-ethyl]-4-fluorobenzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-((R)-1-ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-((R)-1-ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2-((R)-1-ethylpyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-2-yl)cabonyl-aminomethyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(4-dimethylaminobutyrylamino)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-((S)-1-ethyl-pyrrolidin-3-ylmethyl)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(3-dimethylaminopropylcarbamoyl)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{[N—((S)-1-ethyl-pyrrolidin-3--

yl)-N-methylcarbamoyl]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{[N—((R)-1-ethylpyrrolidin-3-yl)-N-methylcarbamoyl]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-((S)-1-ethylpyrrolidin-2-yl)ethylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-((R)-1-ethylpyrrolidin-2-yl)ethylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(3-N,N,-diethylaminopropylamino)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{[((R)-1-ethylpyrrolidine-2-yl)carbonyl-amino]methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[(1-ethylazetidin-3-ylmethyl)amino]benzene-sulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-((Z)-3-diethylaminoprop-1-enyl)benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aS,7bR)-5-[2-((Z)-3-diethylaminoprop-1-enyl)benzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{N—[((R)-1-ethylpyrrolidine-2-yl)carbonyl]-N-methylaminomethyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{N—[((S)-1-ethylpyrrolidine-2-yl)carbonyl]-N-methylamino-methyl}-4-fluorobenzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(4-dimethylaminobutylamino)-4-fluorobenzenesulfonyl-amino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((R)-1-ethylpyrrolidin-3-ylmethyl)amino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-3-ylmethyl)amino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(4-ethyl-2-oxopiperazin-1-ylmethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-(1-ethylpiperidin-4-ylmethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-(1-ethylazetidin-3-yl)ethyl]-4-fluorobenzenesulfonyl- amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((S)-1-azabicyclo[2.2.2]oct-3-yl)amino]benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((R)-1-azabicyclo[2.2.2]oct-3-yl)amino]benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{[((S)-1-ethylpyrrolidine-3-carbonyl)-amino]methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-((R)-1-ethylpyrrolidin-3-ylamino)ethyl]-4-fluoro-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((R)-1-ethylpyrrolidin-3-yl)amino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[((S)-1-ethylpyrrolidin-3-yl)amino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-(2-{[((R)-1-ethylpyrrolidine-3-carbonyl)amino]-methyl}-4-fluoro-benzenesulfonylamino)-1,1a,2,7b-tetrahydro-cyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-[2-((Z)-3-diethylamino-2-methylprop-1-enyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-((R)-1-ethylpyrrolidin-3-yl)ethylamino]-benzenesulfonylamino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aRS,7bSR)-5-{2-[2-((S)-1-ethylpyrrolidin-3-yl)ethylamino]-benzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-((S)-1-ethylpyrrolidin-3-yloxymethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-((R)-1-ethylpyrrolidin-3-yloxymethyl)-4-fluoro-benzenesulfonylamino]-1,1a,2,7b-tetrahydro-cyclopropa-[c]chromene-4-carboxylic acid; (1aR,7bS)-5-[2-(1-ethylpiperidin-3-ylmethyl)-4-fluorobenzene-sulfonylamino]-1,1a,2,7b-tetrahydrocyclopropa[c]chromene-4-carboxylic acid; (1aR,7bS)-5-{2-[2-((R)-1-ethylpyrrolidin-2-yl)ethyl]-4-fluorobenzenesulfonyl-amino}-1,1a,2,7b-tetrahydrocyclopropa-[c]chromene-4-carboxylic acid; and a pharmaceutically acceptable salt or stereoisomer thereof.

12. A pharmaceutically acceptable composition comprising a compound of claim **1** and a pharmaceutically acceptable excipient.

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